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EDITORS
P. R. EVANS and I. A. B. CATHIE

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OBITUARY

SIR
Leonard Gregory Parsons

F.R.S., M.D., F.R.C.P., F.R.C.O.G.

Walter Stoneman, London

LEONARD PARSONS was born in Worcestershire on November 25, 1879, educated at King Edward's Grammar School, Birmingham, and studied medicine at Birmingham University. He graduated M.B., B.S., London, in 1903, proceeding to his M.D. degree five years later. His first resident appointment was at Queen's Hospital, Birmingham, and this was followed by a few years in general practice. He often referred to this part of his professional life with pride and satisfaction, and would say how invaluable that experience had proved to be to him throughout the whole of his professional career. Then, with this background, he turned to what was to be his main absorbing interest for the rest of his life. He became a resident medical officer to The Hospital for Sick Children, Great Ormond Street, London, and later, casualty officer. The latter was to be a short, but as he always acknowledged, profitable experience of paediatric surgery.

He was appointed Physician to Out-Patients to Birmingham Children's Hospital in 1910, when this was a small voluntary hospital with only 62 cots and not part of Birmingham University. Parsons, even at this early stage of his career, had realized that the diseases and disorders of infancy and childhood was a much neglected subject and he set himself the task of correcting this with energy and enthusiasm. Within as short a period as five years, he had so impressed his university colleagues of the importance of this subject that he was appointed Lecturer in Diseases of Children, a post specially created for him. He had already begun to study, investigate, and write on paediatrics, and one of his first important communications was the Arris and Gale Lecture before the Royal College of Surgeons in 1912. The subject of this address was 'The Mechanism and Treatment of Shock' and was based on studies carried out in association with Mr. Tyrrell Gray during the time they had been working together in London. Disorders of growth and nutrition soon attracted his interest and enthusiasm, and his determination to extend knowledge and understanding of this subject remained unabated for the next 40 years. His paper on 'Infantilism Associated with Chronic Interstitial Nephritis' in 1911 was an early and important contribution to some of the features of renal rickets which was not very widely recognized at that time.

During the 1914-18 war Parsons served overseas with the Royal Army Medical Corps as medical specialist to a military hospital in Serbia and consultant physician to the Serbian Army. For these distinguished services he was awarded the Order of St. Sava.

On demobilization in 1918, he returned with renewed vigour to his work for children. Soon afterwards the Children's Hospital, which had moved to new and larger buildings, was recognized for the training of students and Parsons began to hold regular clinical and tutorial classes, which were largely attended and welcomed by the undergraduates. In 1923, he was elected a Fellow of the Royal College of Physicians and appointed Goulstonian Lecturer: the subject he chose for these lectures was 'Some Wasting Disorders of Infancy.' Further evidence of his research work

on nutrition was given when he delivered the Ingleby Lectures in Birmingham University in 1928 on ' Recent Advances in our Knowledge of Rickets and Allied Disorders,' and he was one of the first to show that rickets could be cured by giving irradiated cholesterol.

From this time onwards a steady stream of important papers came from his pen. Coeliac disease and the anaemias of infancy were two subjects in particular which he, with his team of associates, subjected to detailed and painstaking investigation. Parsons was one of the first, if not the first, to demonstrate that hydrops foetalis, icterus gravis, and haemolytic disease of the newborn, were merely different clinical manifestations of an underlying haemolytic process of unknown aetiology. This was in 1933, and these investigations and demonstrations paved the way for the work of Levine and others who established the significance of the Rh factor six years later. His investigations into fat metabolism and coeliac disease formed the subject of the Ratchford Memorial Lecture in the University of Cincinnati in 1931. Ascorbic acid was first synthesized by Sir Norman Haworth, Professor of Chemistry, University of Birmingham, and in 1933 Parsons demonstrated to the Royal Society of Medicine the first case of scurvy successfully treated with ascorbic acid.

While on a visit to America in 1925 he met Abraham Flexner who had written that modern paediatrics was unknown in Great Britain except in Glasgow. Parsons was determined that he would force Flexner to retract this statement which he was able to do in a comparatively short time. Indeed, the national and international reputation that the Birmingham Medical School now holds in the sphere of paediatrics has been gained by Parsons' leadership, foresight, and wise guidance. The extension to the wards and special departments of the Children's Hospital have been due almost entirely to his initiative and direction. He was Chairman of the Committee of Management of the Hospital in 1939 and much of the work for the planning and designing of the infants' wing devolved on his shoulders. These buildings, the like of which exist nowhere else in this country, were conceived by him in 1929 and completed in 1940. In March, 1947, at a special dedication ceremony, this building was named the ' Leonard Parsons Block ' and will thus remain a perpetual memorial to his work on behalf of paediatrics and Birmingham University.

In his endeavours still further to promote the study and recognition of paediatrics and child health, Parsons was actively interested in establishing the Diploma of Child Health of the Royal Colleges in 1935, and he acted as one of the examiners for several years.

During all these years Parsons was steadily establishing an international reputation as a brilliant and outstanding paediatrician, and prizes and awards began to be bestowed upon him in steadily increasing numbers. He was elected Vice-President of the International Paediatric Congress at Stockholm in 1930, delivered the Ratchford Memorial Lecture at the University of Cincinnati in 1931, and the Blackader Memorial Oration before the Canadian Medical Society in 1946. In this country he was President of the Children's Section of the Royal Society of Medicine in 1932, William Withering Lecturer, Birmingham University, in 1937, and Dawson Williams Memorial Lecturer and prize winner in 1938. He was an original member of the British Paediatric Association, and as President from 1942 to 1945 he played an active role in extending its activities and enhancing its prestige. Despite all these multifarious and onerous medical activities and responsibilities, Parsons maintained a freshness and a sense of responsibility for medical education and was taking his full share in the work and activities of Birmingham University. As has already been said, when he joined the staff of the Birmingham Children's Hospital there was no place for the teaching of paediatrics in the curriculum of the medical students. In 1934, clinical clerking in the Children's Hospital was made compulsory for all students in their final year, and in 1943 paediatrics was made a special and distinct part of the final examination, Birmingham being one of the first universities in this country to adopt this course.

The outbreak of the second world war produced almost a revolution in Parsons' professional activities, and to a man of lesser merit and ability might have had most unfortunate consequences. At this time he was Professor of Children's Diseases, Subdean of the Medical Faculty, a Councillor of the Royal College of Physicians, London, and busily engaged in practice, teaching, and research. He accepted, in addition to all these responsibilities, the onerous task of Medical Officer for the Midland Region and here his exceptional ability was directed into administration in most difficult and trying times. These served as fresh fields for his fertile and imaginative mind, and under his wise, astute guidance the organization ran smoothly and efficiently and was able to deal with large numbers of wounded service men and air-raid casualties. His advice was frequently sought by the medical staffs of the hospitals, the medical services of the Army, the Air Force, and the Ministry of Health. His tact and capacity for unremitting hard work,

earned him the respect and gratitude of all concerned. He did not, however, permit these administrative responsibilities to divorce him from active clinical work, but continued to maintain an energetic interest in child welfare. In 1942, he was awarded the Moxon Medal of the Royal College of Physicians, given ' to the person who is deemed to have most distinguished himself by observation and research in clinical medicine,' and the following year he delivered before the College the Charles West Lecture on the ' Prevention of Neonatal Disease and Neonatal Death '.

Before the end of the war Parsons was appointed Dean of the Faculty of Medicine in Birmingham, when the problems and difficulties of undergraduate instruction were formidable due to overcrowding and depleted staffs. The fact that the standard was not only maintained but the number of students increased was due in no small measure to his administrative skill. The war over, the return of the various departments to a peace-time footing and their desires for improvement and expansion, as well as the establishment of full-time University clinical departments, demanded a steadily increasing amount of his time and thought. He carried the burden of these responsibilities with equanimity, and the smooth and satisfactory manner whereby many of the schemes came to fruition gave still further evidence of his genius for administration.

Reference must also be made to the part he played in the promotion of the Birmingham Institute of Child Health. In 1930, at his instigation, discussions were inaugurated between the University and Birmingham City Council to formulate a plan to fuse and integrate the preventive and curative aspects of child health. Initially progress was slow and negotiations were also held up by the war, and it was not until 1945 that his plan was finally approved by Birmingham City Council, the University, and the Children's Hospital. This Institute, whose Council is composed of representatives appointed by these three bodies, fulfilled Parsons' ambitions, and the scheme he had evolved was the first complete one in this country. He remained an active and much valued member of the Council up to the time of his death.

Parsons' pre-eminent services to his country received national recognition in 1946 when he was knighted. During the last few years he had been the recipient of many further honours and awards. In 1947 he was elected a Fellow of the Royal College of Obstetricians and Gynaecologists and in 1948 a Fellow of the Faculty of Radiologists. The award he valued highest, not so much for himself but for Birmingham University and the medical profession, was his election to the Fellowship of the Royal Society two years ago. He was Harveian Orator to the Royal College of Physicians for 1950, and a few days before his death he delivered the Harben Lectures to the Royal Institute of Public Health and Hygiene.

This sketchy and incomplete representation of some aspects of Sir Leonard Parsons' professional career, attainments and honours, fails to give any real indication of his character, individuality, and great gifts. He had a gentleness, a kindness, and a tolerance that remained unblemished and was never altered by the many awards and recognitions of his eminence. He remained a simple and a humble man, in some ways shy and retiring, and he never sought publicity. He never allowed himself to be ruffled or hurried, but remained calm and imperturbable whatever the circumstances might be. His high moral character, his earnestness of purpose, and his scrupulous honesty and open-mindedness endeared him to all and won many to his side. At the same time Parsons had vision and imagination, but his opinions were always practical although fundamental principles were uppermost in his mind. He had determination to accept nothing but the best, and having so made up his mind he would strive to achieve the objective and could be a forcible and powerful opponent to compromise. His mind was clear, quick, and lucid; he had a very retentive memory and his powers of sustained concentration were nothing short of remarkable. He had flexibility of intelligence, vigour, and energy which were intrinsic features of his genius. He was a deeply and earnestly religious man, and would never stoop to any action that might even appear to be mean, underhand, or unjust.

Sir Leonard Parsons was spared ill-health, pain or suffering. He died swiftly and unexpectedly on a Sunday morning (December 17, 1950) after his customary attendance at church, in his own home and surrounded by his family.

Paediatricians the world over will mourn the passing of a truly great and noble man; few, if any, have done as much as he to promote the welfare of infants and children during the last half century.

J.M.S.

A DIETETIC APPROACH TO THE COELIAC AFFECTION

BY

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From The Hospital for Sick Children, Great Ormond Street, London

(Received for Publication February 8, 1950)

The coeliac affection occurs among children of all financial grades of the population, making its appearance some time between the ninth month of life and the end of the second year. Its incidence has been on the increase since before 1939, partly, no doubt, due to a more frequent recognition of its features. The war cannot be entirely blamed as, both during hostilities and since, food rationing has provided a better balanced diet in many homes, and more intense propaganda on food values has been provided by child welfare clinics.

The traditional method of treatment, concentrating on reduced fat intake, was unsatisfactory, leading by a lengthy and laborious progress to an often imperfect recovery. Some improvement in results followed the high vitamin B therapy of May, McCreary, and Blackfan (1942), but there was still a large residuum of complete or partial failures and of recurrences. It was decided, therefore, during the war, to investigate the treatment advocated by Bircher-Benner (1935) who, in his Zurich clinic, had obtained good results with a fruit and vegetable diet. A case of coeliac disease, first diagnosed at 3 years of age, had been placed on this diet at the age of 6 years, and gained 14 lb. in eight months with an increase in height of three inches. Similar, though modified, treatment had been introduced by Feer (1929) at the Kinderklinik, Zurich, and later continued by his successor, Fanconi. Fanconi (1930) referred to favourable results in 50 typical cases of coeliac disease treated with the fruit and vegetable diet.

The present report describes the treatment of 25 cases of coeliac disease. The first 19 of these were given the fruit and vegetable diet advocated by Bircher-Benner (Bircher-Benner diet).* At first this diet was followed exactly, but with the passage of time disadvantages became evident and eventually only nine cases continued on the strict regime. The diet of four cases had to be modified by the addition of appreciable amounts of protein, and two cases relapsed and died. Gradually a new diet was evolved, being a modification of that used by Fanconi. Four cases not responding well to the Bircher-Benner diet were changed on to this, and then a further six fresh cases were treated immediately on diagnosis.

The diagnostic criteria used for the cases in this therapeutic trial were those given by May (in Garrod, Batten, and Thursfield 1947): (1) onset of symptoms six months or later after birth; (2) characteristic pultaceous, putty-coloured faeces; (3) anorexia and failure to gain, or actual loss, in weight, and wasting of muscles; (4) distension of abdomen; (5) impaired absorption of fat; (6) blood sugar rise of less than 40 mg. % in the oral glucose tolerance test; (7) normal trypsin enzyme content of pancreatic secretion; (8) no evidence of chronic infection, anomaly of intestines, parasitic infestation, or fibrocystic disease of the pancreas.

All cases fulfilled these criteria except that in the first seven, which had been unsuccessfully treated previously, the laboratory investigations were not quite complete.

The criteria of progress adopted were: return of appetite; improvement in the nature of the stools; reduction in girth; increase in weight and height; maintenance of normal level of haemoglobin and protein in the blood.

There are other changes which are obvious to the nurses and physicians, such as greater happiness and contentment, and the healthier appearance of the child as shown by the improved texture of skin and hair and increase of muscular tone. These factors, not being susceptible of measurement, have not been used in assessing progress.

The Bircher-Benner Diet

Briefly this diet consists of a preliminary short period of three to six days in which only raw fruit and vegetable juices are given. Then, in stages, nutmilk (diluted nutcream); fruit, grated or as puree; raw fruit porridge (Muesli), grated vegetables, and a cooked vegetable soup with added soya flour are given. Next salads of shredded or grated root vegetables, shredded fruit, and leaf vegetables and cooked vegetables either in soup or as

*This was prepared under the direction of Mrs. C. Loewenfeld.

a puree are added. The diet is alternated with three days of only raw food and three days with added cooked foods with a transition day between. Honey is given almost from the start, and as soon as nutmilk is given 'enervyte,' a wheat germ concentrate containing the vitamin B complex, is added. Later further additions are made such as cream cheese, stewed fruit, rusks, wholemeal bread with a little butter, potatoes, macaroni, egg (once a week), and a little meat twice a week. Each addition is made separately—at first in small and then in gradually increasing quantities—the effect on the stools, appetite, and general condition being the guide. Finally the number of 'raw days' is reduced to one or two a week.

It will be seen that to start with the diet consists only of soluble proteins, carbohydrates, and salts. The early addition of nutcream increases the calorie intake by adding fat and protein. Until this stage has been reached the calorie intake is deficient, as also is the protein. In the final stages of the diet the calorie and protein intake is adequate, but the calcium is lower than in the average diet. The vitamin D content is also low, and in the usual absence of adequate sunlight regular exposure to ultra-violet light is needed.

Nineteen cases were treated initially with this diet, and the records of their gain in height and weight compared with the expected gains are shown in Figs. 1-19. After a stay in hospital on the diet, varying between three months and two years, the children were sent home or to a suitable convalescent home. The length of stay varied owing to a variety of reasons. In general, each child was sent home when fully established on the diet, but because of the war some children could not be found suitable homes and their stay was prolonged. In other cases intercurrent infections caused setbacks. Many cases returned for a further period of treatment, usually because of failure to maintain the diet at home.

Results of Treatment

The result of the treatment can be divided into three phases: (1) immediate, the first few weeks; (2) intermediate, the succeeding months in hospital; (3) late, the fate of the children on leaving hospital.

Progress was regarded as good only if the rates of increase of height and weight equalled those expected for the age.

Immediate Phase. In the first few weeks there was in all cases a considerable loss of weight of between ½ and 2½ lb., with a reduction of girth and a marked improvement in the stools. The general condition of the child sometimes deteriorated, and gave rise to some anxiety in a few cases which were in a poor condition to start with. The rapid loss of weight appeared to be due to two factors, the partial starvation and the decrease in the large mass of fermenting intestinal contents, as shown by the stools changing from pale, loose, and bulky, to dark brown, firm, and small. It was considered that much of the immediate improvement was due to the relief of the distension.

Intermediate Phase. A feature of this phase was a marked fall in plasma protein levels—to 4% or less, often with oedema. This occurred in nine cases, and in most of them necessitated plasma transfusion. The haemoglobin at the beginning of treatment was under 80% in all but three cases. Under treatment it fell further in four cases and subsequently rose again, but in only ten did it finally exceed 80%. No case of severe anaemia or megalocytic anaemia occurred.

Late Phase. This phase, at home, was, as was to be expected, often not so successful as in hospital, particularly as in the last years of the war and the first post-war years when this part of the work was being done special diets were difficult to obtain and were expensive. Relapses occurred, sometimes with oedema or low plasma protein levels. Slight clinical rickets was observed once in this phase and one other patient had a raised plasma phosphatase level.

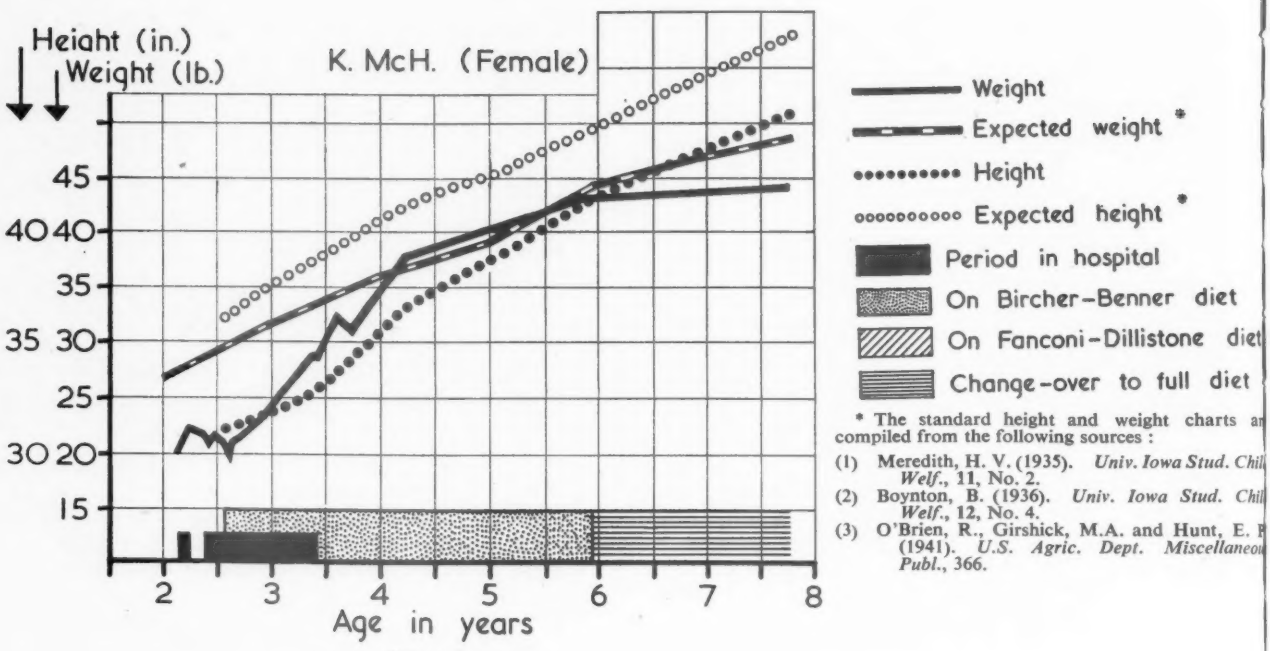
TABLE 1
RESULTS OF BIRCHER-BENNER DIET

Intermediate Phase	Late Phase		Figs.
Good .. 12	Good, no relapse	7	1–7
	Relapsed, diet modified, good	2	8–9
	Relapsed, changed to new diet, good	2	10–11
	Relapsed, died	1	12
Poor .. 7	Good, picked up at home ..	2	13–14
	Relapsed, diet modified, good	2	15–16
	Relapsed, changed to new diet, good	2	17–18
	Died	1	19

SUMMARY OF FINAL RESULTS

Good progress on original diet	9
Good progress after modification of diet by increase of protein	4
Good progress after change to new diet	4
Died	2

A survey of these cases showed the following advantages and disadvantages of the Bircher-Benner diet.



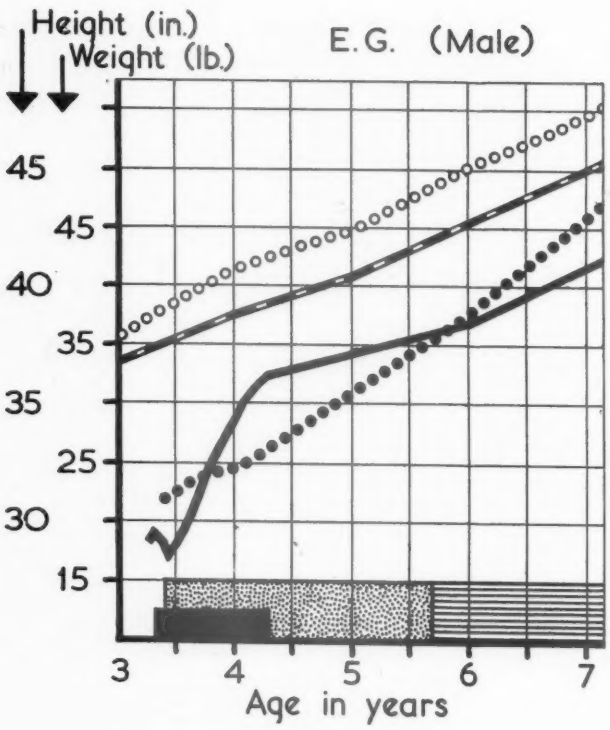
* The standard height and weight charts ar compiled from the following sources :

(1) Meredith, H. V. (1935). *Univ. Iowa Stud. Chil Welf.*, 11, No. 2.

(2) Boynton, B. (1936). *Univ. Iowa Stud. Chil Welf.*, 12, No. 4.

(3) O'Brien, R., Girshick, M.A. and Hunt, E. P (1941). *U.S. Agric. Dept. Miscellaneou Publ.*, 366.

FIG. 1.



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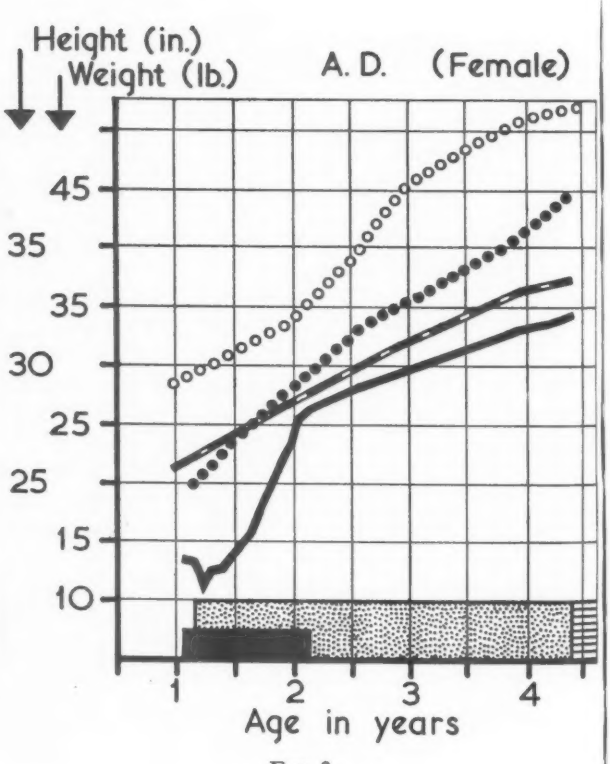

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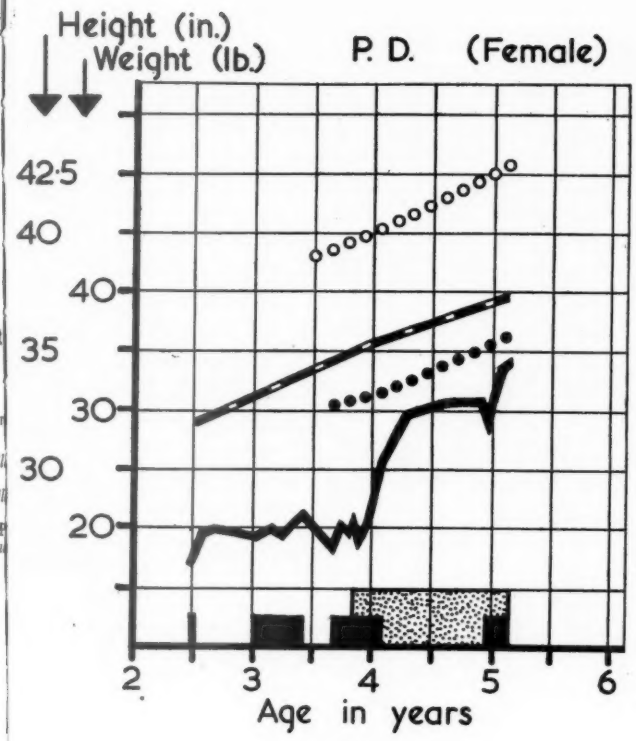

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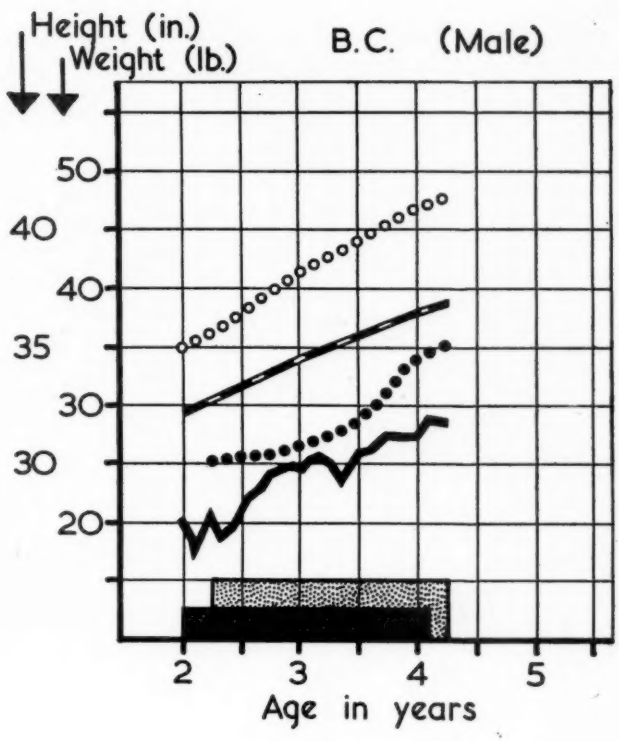

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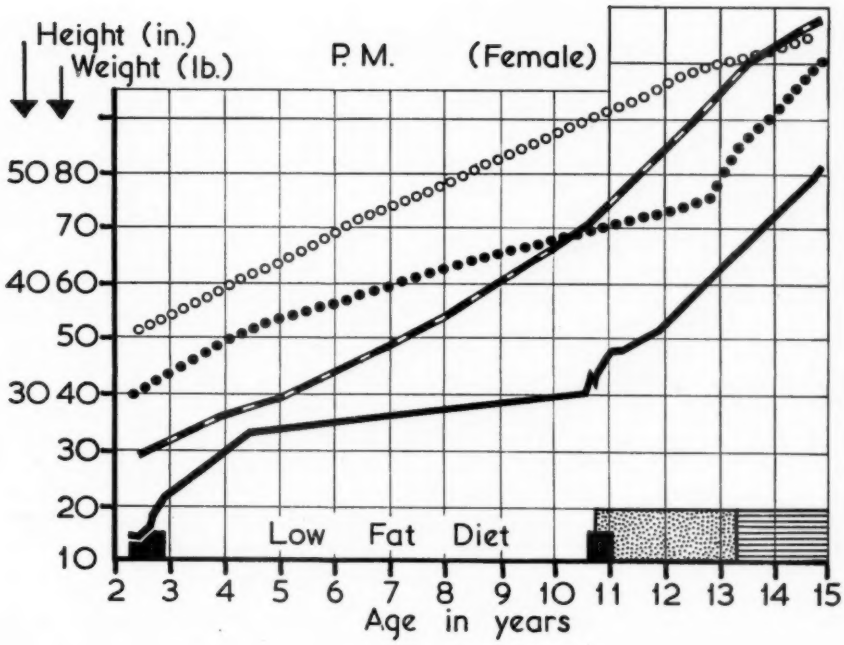

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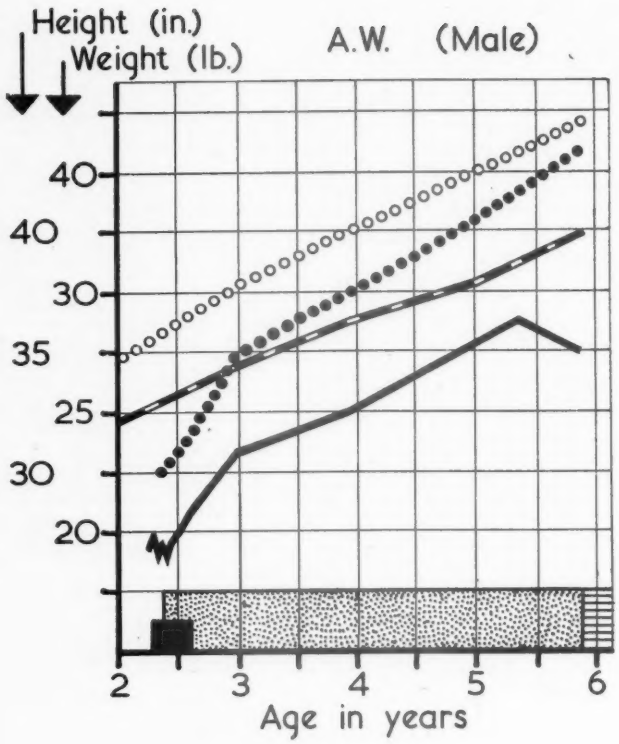

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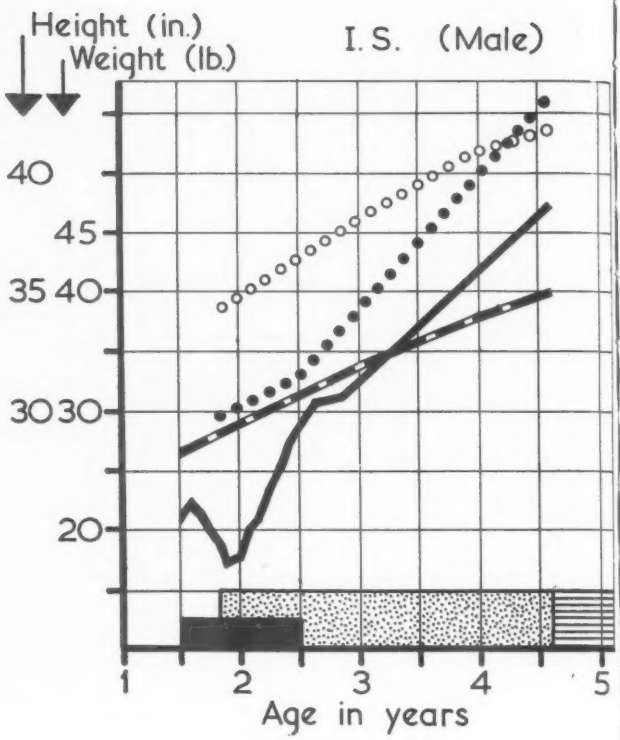

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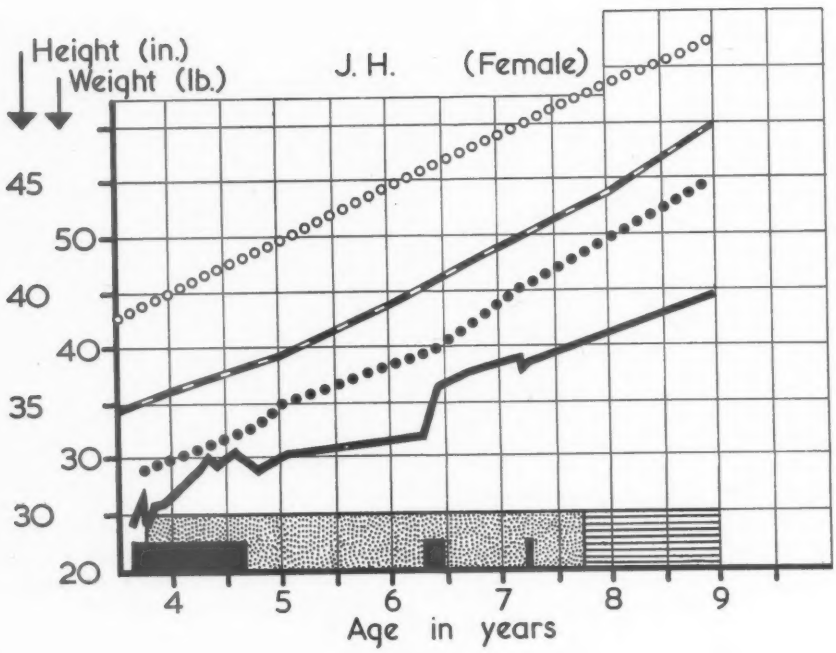

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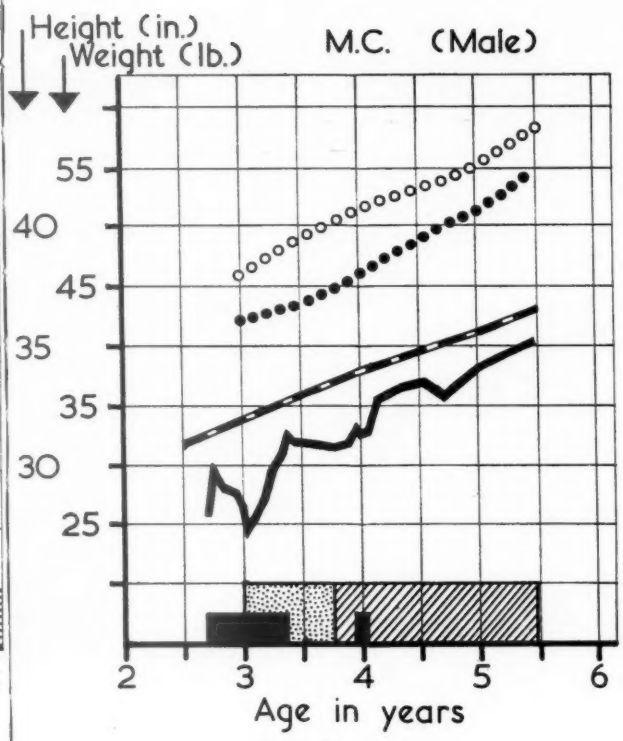

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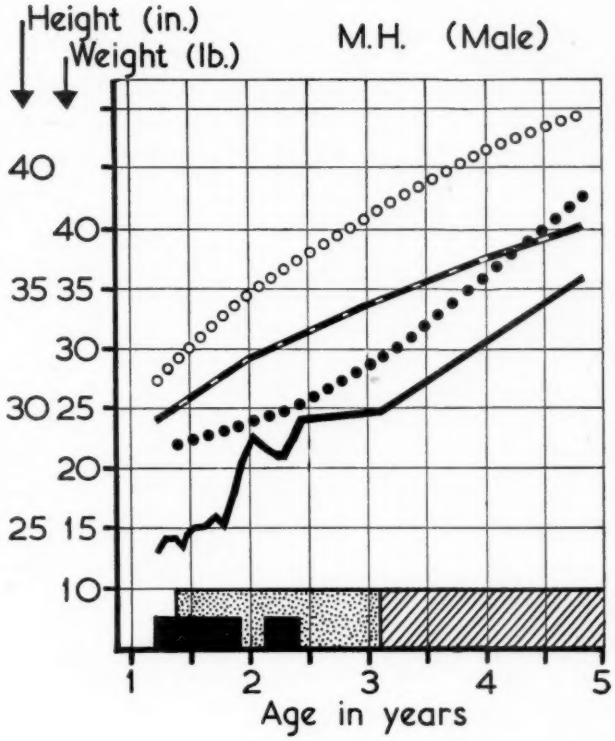

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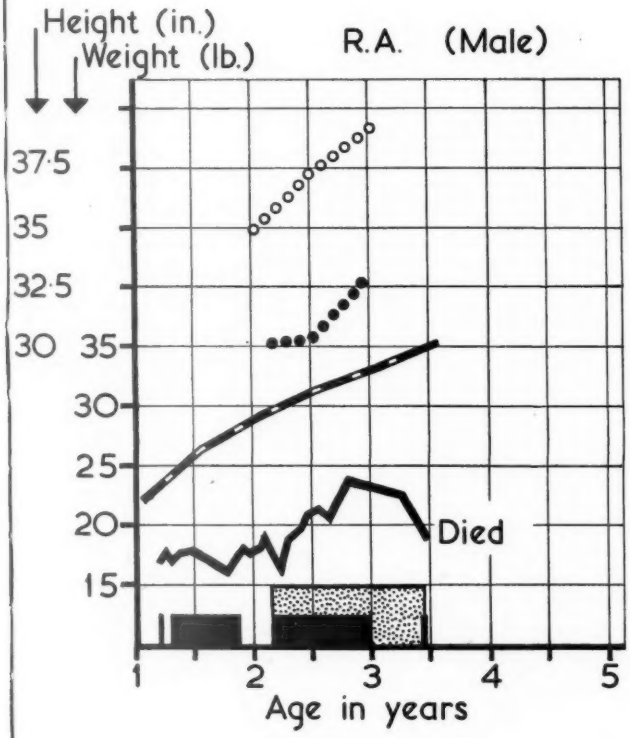

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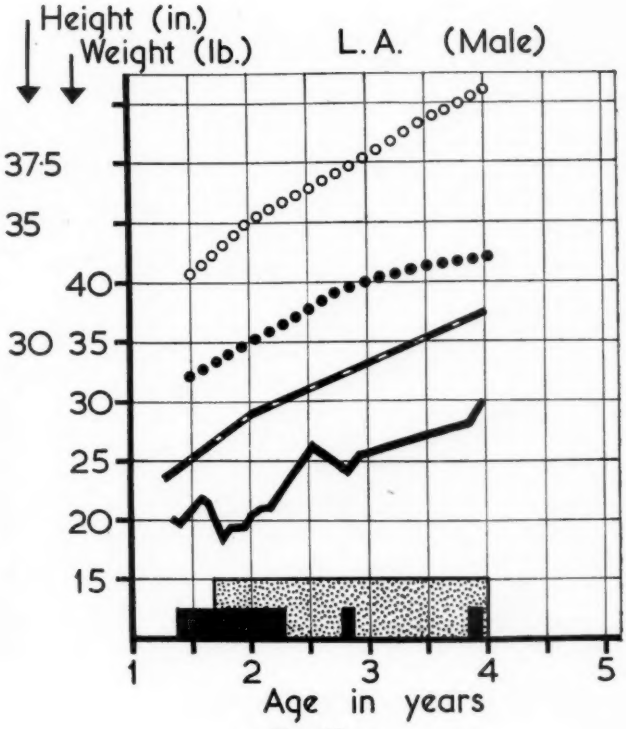

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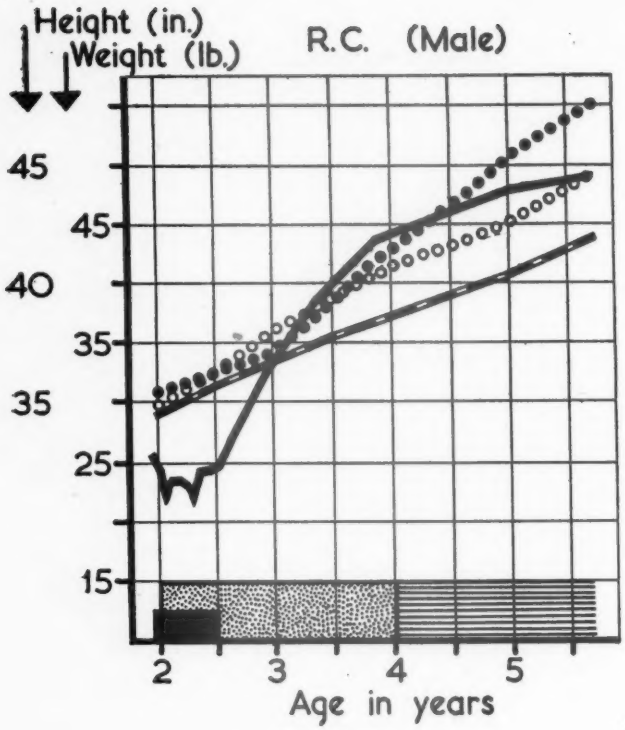

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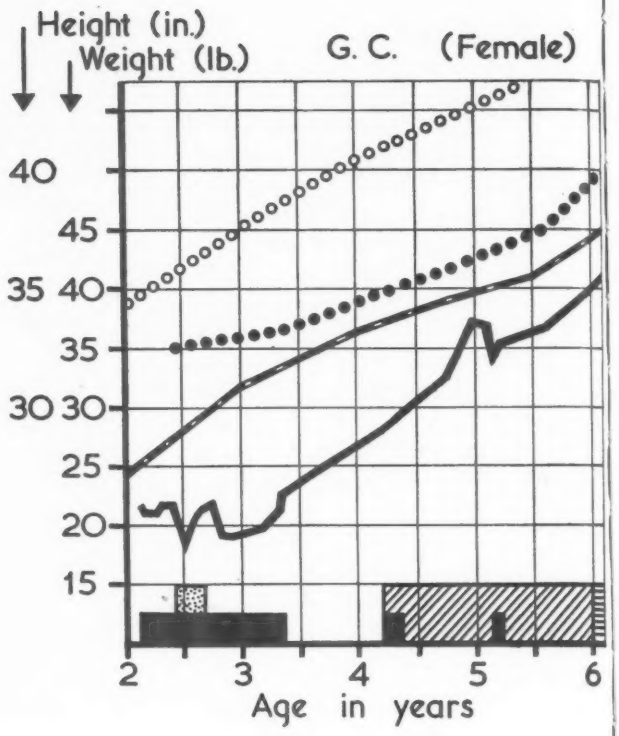

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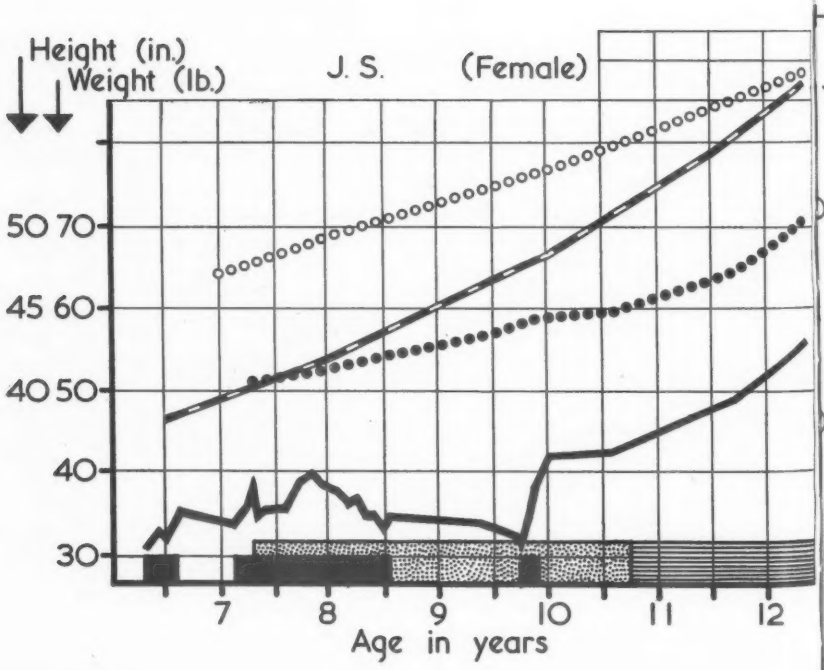

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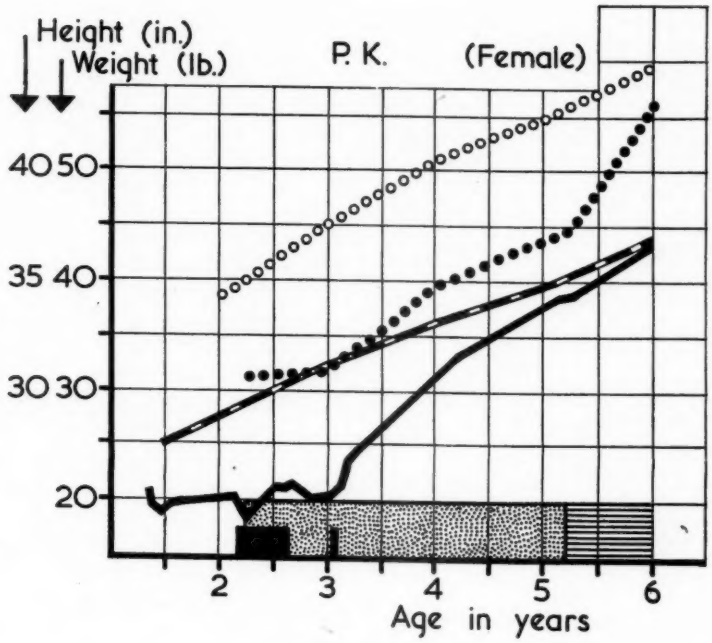

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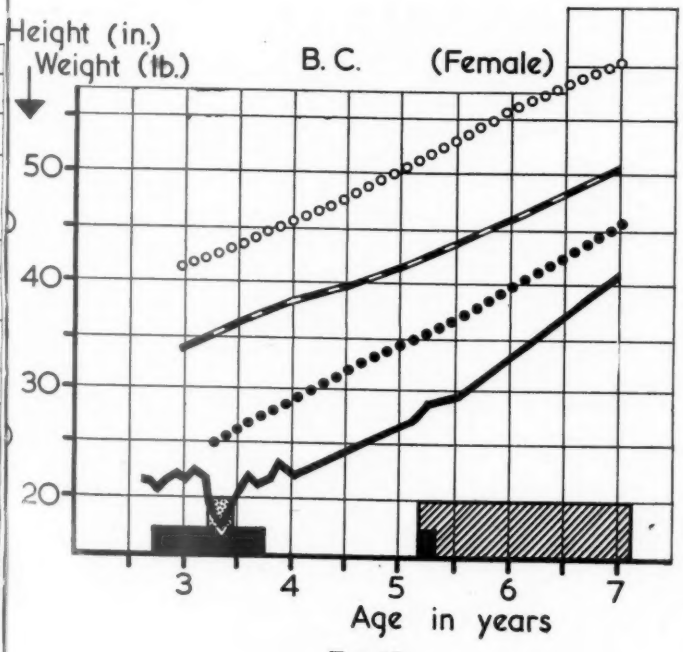

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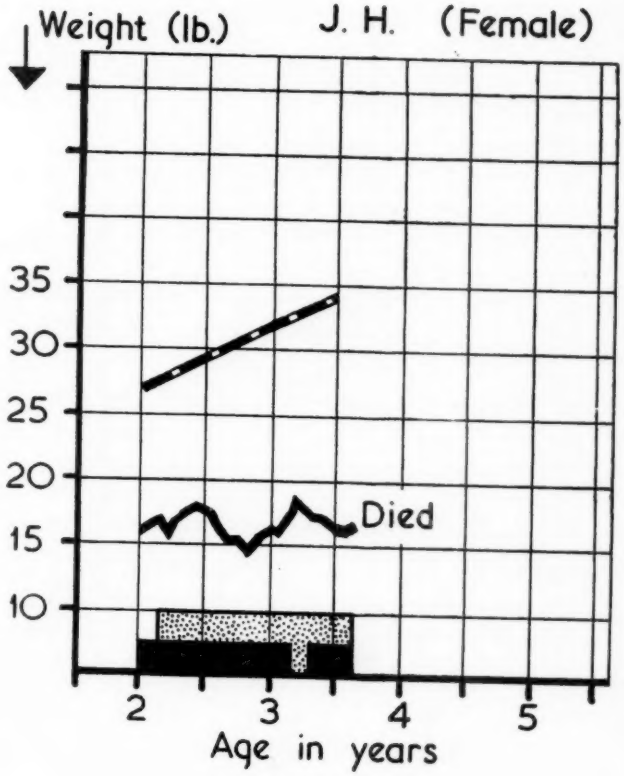

FIG. 19.

Advantages. Control of the distension and of the fermenting and loose stools is rapid and certain. This in turn improves the temper and well-being of the patient. The stools become chemically normal. The diet provides an easily assimilable supply of fat, carbohydrate, and protein.

Disadvantages. Initial semi-starvation is too prolonged, leading to an unnecessary degree of collapse. The introduction of protein is too slow, leading to low plasma protein levels and oedema and in three cases delaying growth; the addition of animal protein is followed by a marked improvement. In fairness it must be admitted that if the child really eats all the diet the mixture of vegetable proteins and the small allowance of animal proteins is, in fact, sufficient in most cases for normal growth. The supply of vitamin D is inadequate.

The diet is complicated, difficult to prepare, and expensive, and many children tire of its large bulk.

The New Diet

As the disadvantages of the Bircher-Benner diet became obvious, a modified diet similar to that used by Professor Fanconi (1937-38) was evolved (Appendix 2). This diet is divided into four stages, the first two being given wholly in hospital.

The duration of stage I is not longer than six to ten days and may be called a 'starvation' phase, providing only 920 calories as against an average of roughly 1,200 calories for an infant of 1 to 2 years of age. It leads to clearing the bowel of its unhealthy contents. Usually a distinct improvement in the temperament of the child and a reduction of abdominal distension is noticeable.

Stage II is maintained roughly for a period of two weeks. Appetite usually improves, and the stools become fewer, less bulky, better coloured, and much less offensive.

Stage III begins in hospital and is continued at home, and may need to be maintained for six to nine months.

The transition to stage IV and onwards to a normal diet is by gradual experimental additions, guided by the tolerance shown by the child's appetite, digestion, and character of the stools. It is at this stage that starch-containing foods are introduced for the first time. Intercurrent infections, mainly respiratory, or intolerance to a particular foodstuff, may necessitate a halt or a regression in the progress of the dietary additions. The necessary vitamin needs are provided in the scheme as outlined.

Six new cases have so far been treated on this diet, and followed up for a period of two to three years. The records of their gain in weight and height compared with the expected average are given in Figs. 20-25. Also four of the cases not doing well on the Bircher-Benner diet were changed over to the appropriate stage of this diet (Figs. 10, 11, 17, 18). All these cases have so far shown no oedema, and plasma protein levels, when estimated, have been normal.

Comment

The diet is usually taken willingly, and the mothers do not complain of its being a trouble to prepare after one or more demonstrations by the hospital dietitian.

The period spent in hospital by the patient is comparatively short, and in most cases he should be back at home on stage III diet within two months of starting treatment. This has obvious advantages as these children so quickly become self-centred and temperamental in hospital and are constantly exposed to the risk of intercurrent infection.

It has been found possible to restore these children to a normal diet mostly within two years, but in two of the cases it would appear that this change was carried out too quickly.

The cost of this diet is not excessive. When special items are obtained through hospitals or clinics the cost has been thus estimated.*

Stage I	.. 15s.	per week
Stage II	.. 18s.	,, ,,
Stage III	.. 22s. 3d.	,, ,,
Stage IV	.. 24s. 4d.	,, ,,

TABLE 2
RESULTS ON NEW DIET

Intermediate Period	Late Period	Figs.
Good .. 6	4	22, 23, 24, 25
Moderate 0	2 (Progress not so good on a normal diet)	20, 21

Summary

A therapeutic trial is described of 19 cases of the coeliac affection treated with the fruit and vegetable diet of Bircher-Benner and followed up for a period of three to six years. Of the 19 patients only nine successfully followed the original regime and have done well. The disadvantages of this diet are outlined, the chief one being the relative shortage of first class protein, leading in many cases to hypoproteinaemia and oedema.

Arising from this trial a new four-stage diet was

* Estimate by Miss Dillistone, Dietitian to The Hospital for Sick Children, Great Ormond Street, London.

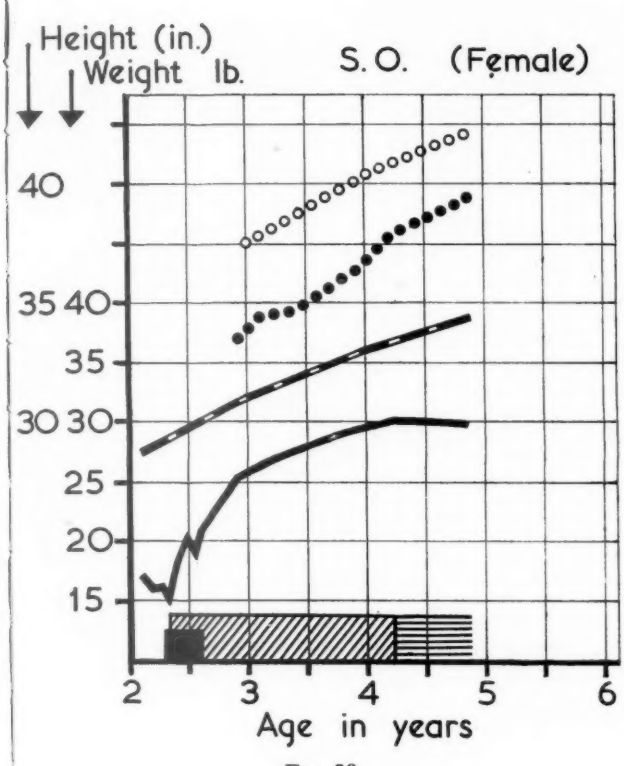

FIG. 20.

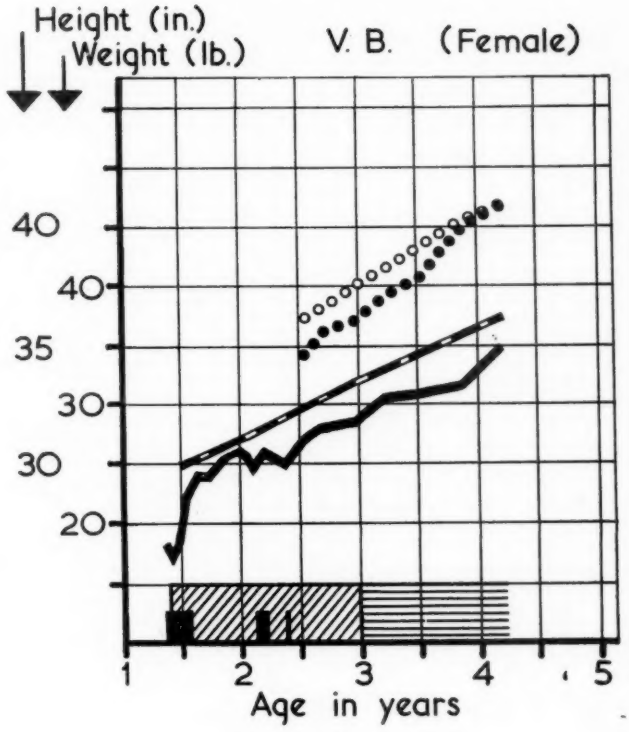

FIG. 22.

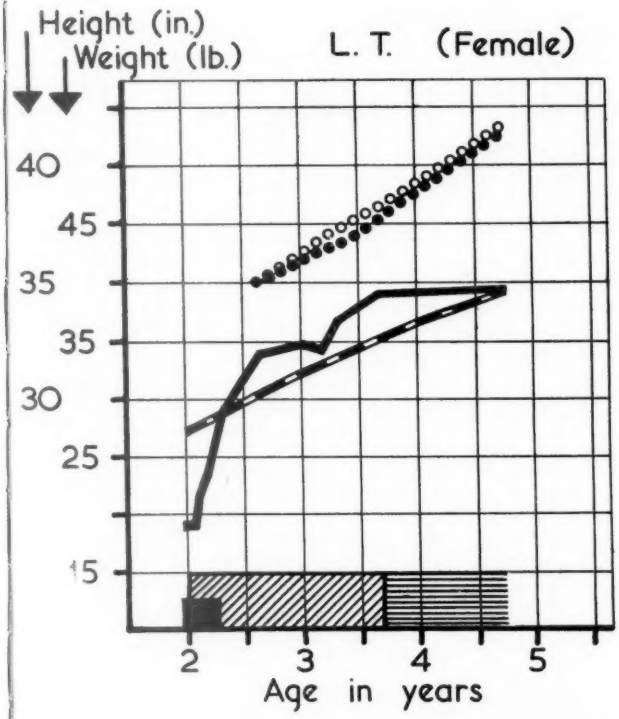

FIG. 21.

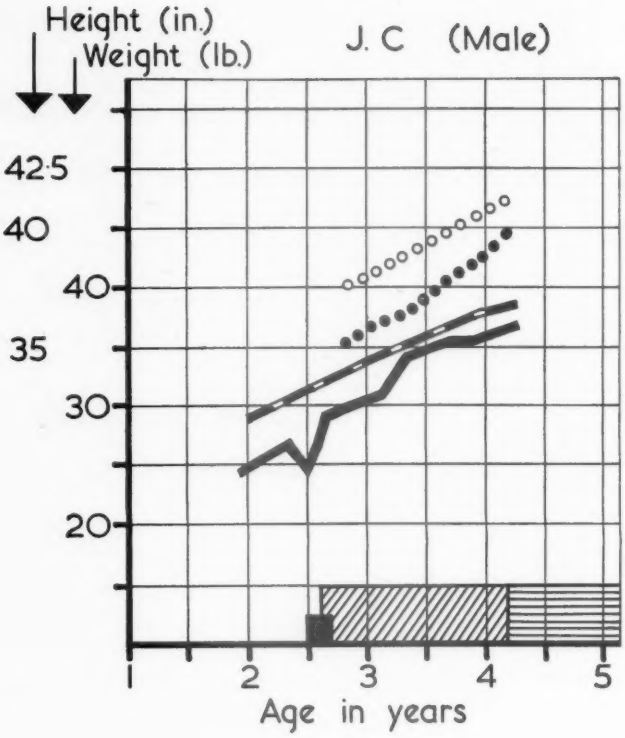

FIG. 23.

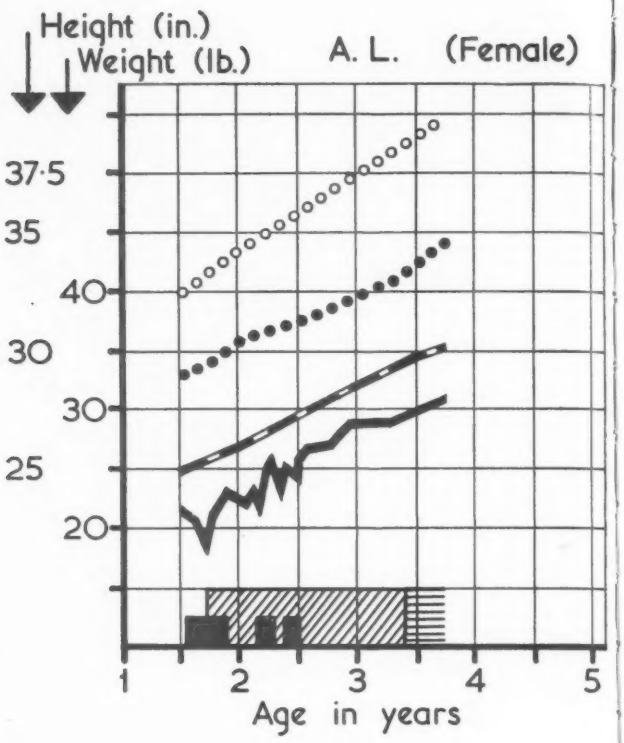

FIG. 24.

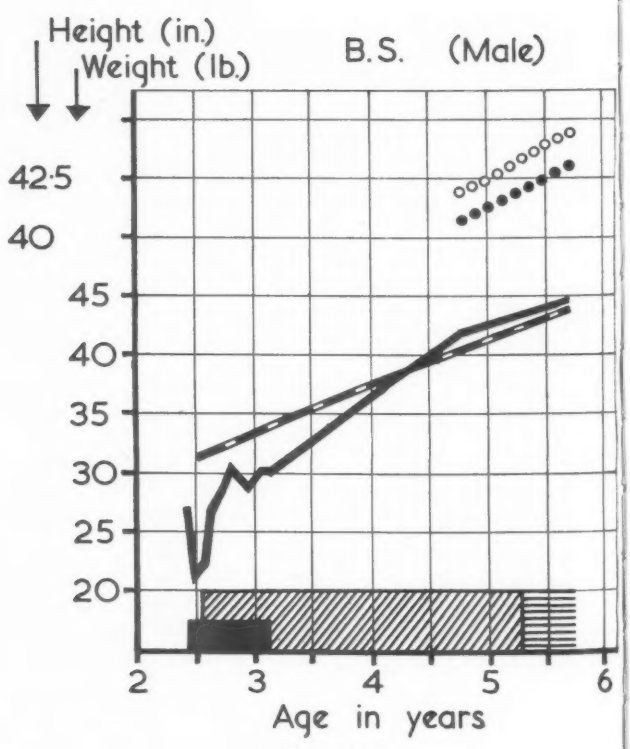

FIG. 25.

evolved and is described, being a modification of that first used by Fanconi. Six new and four old cases have been treated with this diet and followed up for a period of two to three years, with results which are encouraging so far.

We wish to acknowledge our thanks to Dr. R. Elgood and Dr. D. Cruickshank for their detailed progress records in cases 1-19, to Mrs. C. Loewenfeld for her constant advice on the Bircher-Benner diets, and to Miss F. Dillistone for her help and advice with the new diet.

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APPENDIX I

The Bircher-Benner Regime

(Modified by Mrs. C. Loewenfeld)

Nutcream: Nut emulsion (C. 23·16, P. 21·77, F. 51·27).

Enervyte: Unprocessed wheat germ.

Apple juice: Pure, unfermented, unsweetened apple juice in bottles.

Rose hip tea: An infusion made by simmering dried soaked rose hips (pods and pips) for 20 to 30 mins.

Raw fruit porridge (Bircher Muesli): 7½-15 g. fine or medium soaked oatmeal mixed with lemon juice, honey, nutcream (prescribed) or milk and 2-5 oz. (60-150 g.) grated apple or mashed fruit (sieved at the beginning).

Rice gruel (or other cereal gruels): 4-6% gruel, made from 2 tablespoons rice (oats, wheat, barley) to 1 pint (600 c.cm.) water, boiled for 20-60 mins.

Fruit juices: Combined from various fruit in season, freshly extracted and sieved.

Vegetable juices: Combined from various vegetables in season, such as carrots and tomatoes as a basis, with smaller quantities of beetroot, celery, lettuce, spinach, brussels sprouts, cabbage, onion, leek, and herbs added.

Children from the age of 16-18 *months onwards*: Four feeds per day at ordinary meal times.

Children under 16 *months and below average weight*: Four-hourly feeds are given and the juices and nutcream supplemented by rice gruel to make up the desired quantity according to the expected weight for the child's age.

All feeds are sweetened with honey to taste.

According to the age and digestive capacity of the child, fresh fruit and uncooked vegetables are given in the form of juice, puree, or grated or chopped in salads, or the fruit may be given whole.

The prescribed quantity of nutcream per meal is distributed over the various uncooked fruit and vegetable dishes of this meal, according to the child's liking.

All freshly expressed undiluted fruit and vegetable juices with or without nutcream are considered as food, not drink, and are fed with a spoon.

Diet Sheet for Stage I (Raw Day: 3–5 Days)

Time	Intake (oz.)	Foods	Protein (g.)	Calories
7 a.m. ..	5	Rose hip tea	0·5	2
	2	Fruit juice		20
	½	Honey		43
9.30 a.m. ..	6	Fruit juice		60
	2	Tomato puree (sieved)	0·6	9
	5	Rose hip tea	0·5	2
	2	Honey		172
12.30 p.m. ..	5	Fruit juice		50
	4	Vegetable juice	1·8	24
	4	Apple juice drink		60
	2	Honey		172
6 p.m. ..	8	Fruit juice		80
	5	Rose hip tea	0·5	2
	2	Honey		172
			3·9	868

DIET SHEET FOR STAGE II (1–3 WEEKS)

	Raw Day	Cooked Day		Raw Day		Cooked Day	
	Intake (oz.)	Intake (oz.)	Foods	Protein (g.)	Calories	Protein (g.)	Calories
7 a.m.	5	5	Rose hip tea	0·5	2	0·5	2
	2	2	Fruit juice		20		20
	½	½	Honey		43		43
9.30 a.m.	6	6	Fruit juice		60		60
	2	2	Tomato puree (sieved)	0·6	9	0·6	9
	5	5	Rose hip tea	0·5	2	0·5	2
	¼	¼	Enervyte	0·8	24	0·8	24
	¾	¾	Nutcream	4·8	144	4·8	144
	2	2	Honey		172		172
12.30 p.m.	5	4	Fruit juice		50		40
	4	3	Vegetable juice	1·8	24	1·3	18
	2	2	Tomato puree (sieved)	0·6	9	0·6	9
	4	4	Apple juice drink		60		60
	1	¾	Nutcream	6·4	192	4·8	144
	1½	1	Honey		129		86
		6	Cooked vegetable soup with soya flour			9·0	120
6 p.m.	6	6	Fruit juice		60		60
	5	5	Rose hip tea	0·5	2	0·5	2
	¼	¼	Enervyte	0·8	24	0·8	24
	¾	¾	Nutcream	4·8	144	4·8	144
	2	2	Honey		172		172
				22·1	1,342	29·0	1,355

DIET SHEET FOR STAGE III (1–12 MONTHS)

	Raw Day	Cooked Day		Raw Day		Cooked Day	
	Intake (oz.)	Intake (oz.)	Foods	Protein (g.)	Calories	Protein (g.)	Calories
7 a.m. Optional	5	5	Rose hip tea	0·5	2	0·5	2
	2	2	Fruit juice		20		20
	½	½	Honey		43		43
9.30 a.m.	4	4	Raw fruit porridge(Muesli)	3·5	100	3·5	100
	4	4	Fruit juice		40		40
	5	5	Rose hip tea	0·5	2	0·5	2
	¼	¼	Enervyte	0·8	24	0·8	24
	¾	¾	Nutcream	4·8	144	4·8	144
	2	2	Honey		172		172
12.30 p.m.	2	2	Grated apple (or whole fruit)		20		20
	4	3	Vegetable juice (or puree)	1·8	24	1·3	18
	3	2	Fruit juice		30		20
	4	4	Apple juice drink		60		60
	¾	½	Nutcream	4·8	144	3·2	96
	½	½	Cottage cheese	4·5	68	4·5	68
	1	1	Honey		86		86
		6	Thick vegetable soup (or puree or stew) *			9·0	120
		2	Spinach puree *			4·2	60
6 p.m.	4	4	Raw fruit porridge (Muesli)	3·5	100	3·5	100
	4	4	Fruit juice		40		40
	5	5	Rose hip tea	0·5	2	0·5	2
	¼	¼	Enervyte	0·8	24	0·8	24
	¾	¾	Nutcream	4·8	144	4·8	144
	2	2	Honey		172		172
				30·8	1,461	41·9	1,577

* Both with soya flour.

In some cases ½–1 oz. wholemeal bread with part of the nutcream.

DIET SHEET FOR STAGE IV (UNTIL DISCHARGE FROM HOSPITAL)

Time	Raw Day Intake (oz.)	Cooked Day Intake (oz.)	Foods	Raw Day Protein (g.)	Raw Day Calories	Cooked Day Protein (g.)	Cooked Day Calories
7 a.m.	5	5	Rose hip tea	0·5	2	0·5	2
Optional	2	2	Fruit juice		20		20
	½	½	Honey		43		43
8-9 a.m.	5	5	Raw fruit porridge (Muesli)	4·4	125	4·4	125
	3	3	Whole fruit (or grated apple or juice)		30		30
		1	Wholemeal bread with			2·4	70
		¼	butter (or nutcream spread)				50
	2	2	Milk	2·0	34	2·0	34
	¼	¼	Enervyte	0·8	24	0·8	24
	¾	½	Nutcream	4·8	144	3·2	96
	2	2	Honey		172		172
12.30 p.m.	3	3	Whole fruit (or puree or juice)		30		30
	4	4	Mixed dressed salad (or vegetable juice)	1·8	180	1·8	180
	4	4	Apple juice drink		60		60
		8	Thick vegetable soup (or puree or stew), with soya flour (or rice, barley, wheat, etc.)			12·0	200
		3	Spinach puree with soya flour and mashed potatoes. 1 egg per week (6·8 g. protein, 80 Cal.)			6·5	100
		½	Cottage cheese			4·5	68
	1		Nutcream	6·4	192		
		3	Sweet made from fruit and nutcream (or cottage cheese)			4·5	150
6.30 p.m.	5	5	Raw fruit porridge (Muesli)	4·4	125	4·4	125
	3	3	Whole fruit (or grated apple or juice)		30		30
		1	Wholemeal bread with			2·4	70
		¼	butter (cottage cream or nutcream)				50
		2	Milk			2·0	34
	5		Rose hip tea	0·5	2		
	¼	¼	Enervyte	0·8	24	0·8	24
	¾		Nutcream	4·8	144		
		½	Cottage cheese			4·5	68
	1	1	Honey		86		86
				31·2	1,467	56·7	1,941

WEEKLY DIETARY REGIME FOR STAGE V (AFTER DISCHARGE)

Monday	Raw day (according to stage IV).
Tuesday	Transitional day (according to stage III 'cooked day').
Wednesday	Cooked day with 1 egg.
Thursday	Cooked day with 1 oz. grated cheese.
Friday	Cooked day with 1 oz. grated cheese.
Saturday	Cooked day with 1 oz. meat.
Sunday	Cooked day with 1½ oz. meat.

Example for 'Cooked Day'

Breakfast Raw fruit porridge (Muesli).
Whole fruit, some dried fruit.
1-2 slices wholemeal bread with butter and honey or nutcream or cottage cheese.
1 cup rose hip tea with honey and milk *or* 2-4 oz. milk.

Mid-day meal Whole fresh fruit.
Mixed dressed salad.
Cooked vegetable dish with potatoes or macaroni or rice with some protein addition.

Mid-day meal (cont.) Sweet from fresh or stewed fruit with cottage cheese or nutcream or top of the milk.
1 glass apple juice drink.

Evening meal Raw fruit porridge (Muesli).
Whole fruit, some dried fruit.
1-2 slices wholemeal bread with butter and honey or nutcream or cottage cheese and tomatoes.
1 cup rose hip tea with honey and milk *or* 2-4 oz. milk.

APPENDIX II

The New Diet

The diet is arranged in four stages. Stage I is a preliminary period of rest for the gastrointestinal tract and supplies fluid, protein, and carbohydrate in a predigested form. This period is from one to four days. Stage II follows and is continued for another four to six days. After the rest period appetite returns and stage III is begun; the calorie value at this stage may be increased by giving larger helpings of food allowed. Starch-containing foods are introduced into stage IV; these may be increased according to the ability of the child to hydrolyse and absorb starch.

The whole of the dietary regime contains a high amount of protein with moderate amounts of fat. The important feature is the choice of carbohydrates, which in the first three stages are selected from the non-starch-containing foods. A starch-free bread sold under the trade name of 'proferin' is now available, also a starch-free flour. Soya bean flour is also starch-free and may be used for the making of puddings and biscuits. Vitamin supplements are given separately.

STAGE I

DIET	C	P	F
Feeds given 4-hourly; number of feeds 5. Amount given at each feed 6 to 8 oz. Fruit juices sweetened with honey given between 10 a.m. and 2 p.m. and 2 p.m. and 6 p.m. feeds.	g.	g.	g.
6 a.m.			
8 oz. 'prosol' 1 in 8	8·0	17·4	—
20 g. glucose	20·0	—	—
10 a.m.			
7 oz. buttermilk	13·2	8·1	2·5
20 g. glucose	20·0	—	—
2 p.m.			
8 oz. 'prosol'	8·0	17·4	—
20 g. glucose	20·0	—	—
6 p.m.			
7 oz. buttermilk	13·2	8·1	2·5
20 g. glucose	20·0	—	—
10 p.m.			
8 oz. 'prosol'	8·0	17·4	—
20 g. 'dextrimaltose'	20·0	—	—
	150·4	68·4	5·0

VITAMIN PREPARATIONS: Halibut liver oil, 10 drops daily. Ascorbic acid, 50 mg., when fresh juices are not available.

Total Calories 920

STAGE II

DIET	C	P	F
Feeds given 4-hourly; number of feeds 5. Amount given at each feed 6 to 8 oz. Fruit juices sweetened with honey given between 10 a.m. and 2 p.m. and 2 p.m. and 6 p.m. feeds.	g.	g.	g.
6 a.m.			
8 oz. 'prosol'	8·0	17·4	—
20 g. 'dextrimaltose'	20·0	—	—
10 a.m.			
7 oz. buttermilk	13·2	8·1	2·5
20 g. 'dextrimaltose'	20·0	—	—
4 oz. banana puree	22·0	1·8	—
2 p.m.			
8 oz. 'prosol'	8·0	17·4	—
20 g. 'dextrimaltose'	20·0	—	—
6 p.m.			
7 oz. buttermilk	13·2	8·1	2·5
20 g. 'dextrimaltose'	20·0	—	—
4 oz. banana puree	22·0	1·8	—
10 p.m.			
8 oz. 'prosol'	8·0	17·4	—
20 g. 'dextrimaltose'	20·0	—	—
	194·4	72·0	5·0

VITAMIN PREPARATIONS: Halibut liver oil, 10 drops daily. Ascorbic acid, 50 mg., when fresh juices are not available.

Total Calories 1,110

Vitamin Preparations

Stages III and IV

Halibut liver oil, 10 drops daily. Ascorbic acid, 50 mg., when fresh juices are not available.

	C g.	P g.	F g.
8 a.m.			
8 oz. ' prosol '	8·0	17·4	—
20 g. ' dextrimaltose '	20·0	—	—
4 oz. sieved banana (dried or fresh)	22·0	1·8	—
½ oz. dextrinized rusks or starch-free bread	11·6	0·8	1·2
¼ oz. butter	—	—	6·0
12 noon			
1 oz. finely minced liver, chicken or beef (very lightly cooked) ..	—	5·5	3·0
2 oz. sieved cooked beetroot ..	5·6	1·0	—
1 oz. sieved cooked spinach, cauliflower or sprouts	0·2	0·4	—
4 oz. raw sieved tomatoes ..	3·2	1·2	—
5 oz. ' yoghourt,' egg custard or junket	7·0	4·5	5·5
½ oz. honey	10·0	—	—
4 oz. fruit puree	10·0	—	—
4 p.m.			
8 oz. ' prosol '	8·0	17·4	—
20 g. ' dextrimaltose '	20·0	—	—
1 oz. soya bean flour biscuits or starch-free bread, ¼ oz. butter	9·5	4·6	5·9
6.30 p.m.			
8 oz. ' prosol '	8·0	17·4	—
20 g. ' dextrimaltose '	20·0	—	—
4 oz. banana puree	22·0	1·8	—
	185·1	73·8	21·6

Total Calories 1,190

	C g.	P g.	F g.
8 a.m.			
8 oz. ' prosol '	8·0	17·4	—
20 g. 'dextrimaltose '	20·0	—	—
½ oz. cornflakes	9·0	3·8	—
½ oz. ' bemax '	5·0	5·0	—
1 oz. national bread toasted ..	15·8	2·4	—
¼ oz. butter	—	—	6·0
1 egg, dried or shell, or 1 oz. grilled bacon	—	6·8	7·0
12 noon			
1½ oz. minced liver, chicken, beef or lamb	—	8·2	5·5
1 oz. mashed potato or 2 oz. cooked beetroot	5·0	—	—
2 oz. cooked chopped spinach, cauliflower or sprouts or salad	0·4	0·8	—
4 oz. sieved tomato	3·2	1·2	—
5 oz. ' yoghourt ' or 5 oz. egg custard or cornflour	7·0	4·5	5·5
½ oz. honey	10·0	—	—
4 oz. fresh or dried fruit ..	10·0	—	—
4 p.m.			
8 oz. ' prosol '	8·0	17·4	—
20 g. ' dextrimaltose '	20·0	—	—
1 oz. national bread toasted ..	15·8	2·4	—
¼ oz. butter	—	—	6·0
' Marmite,' honey or jam ..	—	—	—
1 oz. soya biscuits or cake made from starch-free flour	9·5	4·6	5·9
6.30 p.m.			
8 oz. ' prosol '	8·0	17·4	—
20 g. ' dextrimaltose '	20·0	—	—
1 oz. national bread toasted ..	15·8	2·4	—
¼ oz. butter	—	—	6·0
½ oz. cottage cheese (5 oz. milk)	—	4·5	5·5
Medium sized apple, pear, orange, grapefruit, banana or grapes ..	10·0	—	—
	200·5	98·8	47·4

Total Calories 1,623

THE ALIMENTARY LESION IN ANAPHYLACTOID PURPURA

BY

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(Received for Publication February 20, 1950)

Widespread visceral lesions were first described as a complication of cutaneous purpura by Willan in 1808, but they were not generally appreciated until the publications of Henoch (1874) and Schönlein (1837) suggested that they constituted a clinical entity. The alimentary changes have been considered comparable to the skin purpura and are frequently referred to as purpura abdominalis.

Table 1
Clinical Picture of 20 Cases of Anaphylactoid Purpura

Case	Age (Years)	Sex	Presenting Signs	Colic	Frank Melaena	Haema-turia	Joints	Other Complications
1	5½	M.	Colic	+		+	+	
2	4	F.	Joint pains				+	
3	10	M.	Colic	+++	+	+		Acute jejunitis
4	6½	M.	Joint pains	++	+		+	
5	2	M.	Rash, haematuria	+		+		
6	11	M.	Convulsions	+			+	Status epilepticus
7	10½	M.	Acute myositis	+	+	+		Severe myositis
8	4	F.	Joint pains				+	
9	2 11/12	M.	Rash					
10	8	M.	Joint pains	+++	+			Colic intussusception
11	4	F.	?	+			+	
12	5½	M.	Joint pains	+			+	
13	7¾	M.	Colic	+			+	
14	10	M.	Joint pains	+		+		
15	9	F.	Rash				+	
16	2	M.	Rash	+		+		
17	6	M.	Colic	++		+	+	Muscle pain
18	10¼	F.	Rash	++		+	+	Do.
19	4½	M.	?	+	+	+	+	Do.
20	4¾	M.	Colic	+++		+		Acute ileitis
20		15 M. 5 F.		16	5	10	12	

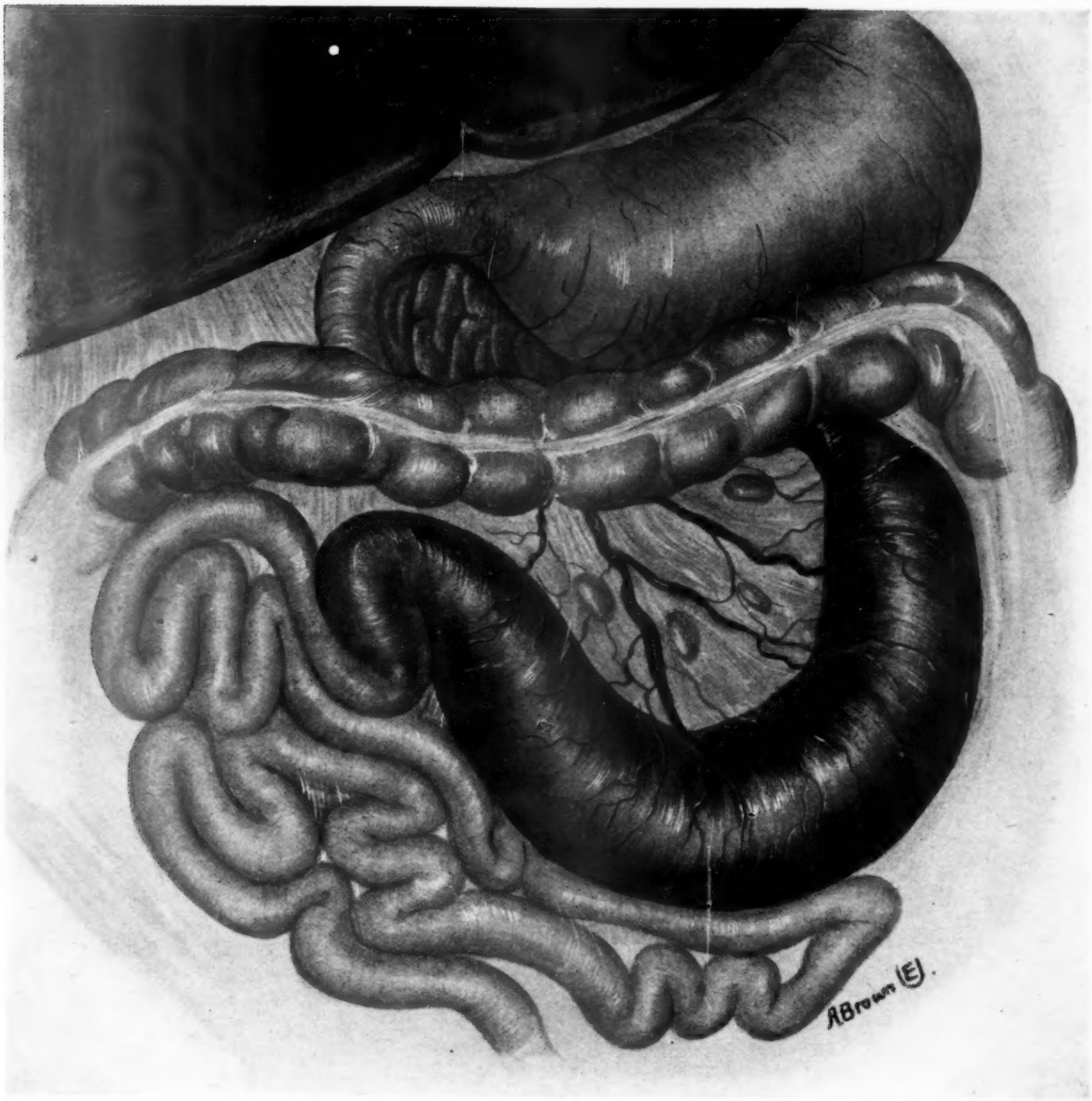

FIG. 1.

They appear to be of transient importance only, and there is no record of progression to chronic disease of the bowel. On the other hand, the renal lesion in anaphylactoid purpura may become indistinguishable clinically or pathologically from Type I nephritis (Ellis, 1949).

The specificity of the bowel lesion has been questioned (Bailey, 1930), but although it has been thought comparable with that seen in a variety of haemorrhagic diseases, there is little evidence that frank haemorrhage occurs in anaphylactoid purpura. In view of the demonstrable specificity of the skin lesion (Gairdner, 1948), it seems desirable to determine the nature of the intestinal changes.

Final opinion will be impossible until adequate pathological studies have been made of the lesion in the acute phase. This is rarely possible, as operation is not usually indicated unless intussusception or perforation complicates the initial damage. For this reason the following case reports are of value in that they illustrate different stages of the lesion. In four of them the bowel was seen at operation, and in another radiological evidence of abnormal peristalsis was available. The cases were all seen during a period of two years at a children's hospital and were part of a total of 20 cases of anaphylactoid purpura admitted during that period.

Table 1 summarizes the clinical picture in the whole group and permits of ready comparison with previous reports.

As would be expected, the standards of admission to hospital ensure that in all cases widespread and often serious complications were present. This contrasts strikingly with the experience of Davis (1948) who found no important complication in 44 cases. Most of these were seen regularly for several years, so it is possible that the severity of the illness varies largely with the individual and not according to any particular phase of the disease process. Hospital experience in general confirms the present series, and the records of Osler (1914) and Gairdner (1948) may be considered representative.

Case Reports

Case 1. J.G., a boy, aged 10 years, was admitted to hospital as an abdominal emergency on October 16, 1948. He had been well until eight days earlier when a transient rash appeared on his chest and abdomen. Two days later he had slight diarrhoea which subsided after three days. Colicky pains then started and gradually became more severe. He vomited frequently and retained no fluid.

STATE ON ADMISSION. The patient was an extremely ill child, grossly dehydrated, with early circulatory failure. The abdomen was not distended. There was diffuse tenderness with some slight localization to the left hypochondrium. Bowel sounds were absent. His condition was urgent and, after pre-operative transfusion, laparotomy was performed.

OPERATION FINDINGS. There was free fluid in the peritoneal cavity. The jejunum was acutely inflamed, bright red, and oedematous (Fig. 1). The segment involved was sharply separated from normal bowel. Obstruction appeared complete and posterior gastro-jejunostomy was performed.

POST-OPERATIVE COURSE. The patient improved steadily, though stomatitis was noted seven days after operation. A barium meal a month later showed a functional stoma and he was discharged from hospital.

He was readmitted on January 2, 1949, when he had a purpuric rash which had first appeared a week previously. This was characteristic of the Henoch-Schönlein exanthem, and involved legs, arms and buttocks (Fig. 2a and 2b). He had no pain and looked healthy. Four days later he complained of severe abdominal pain and began to vomit. The vomiting increased and was later

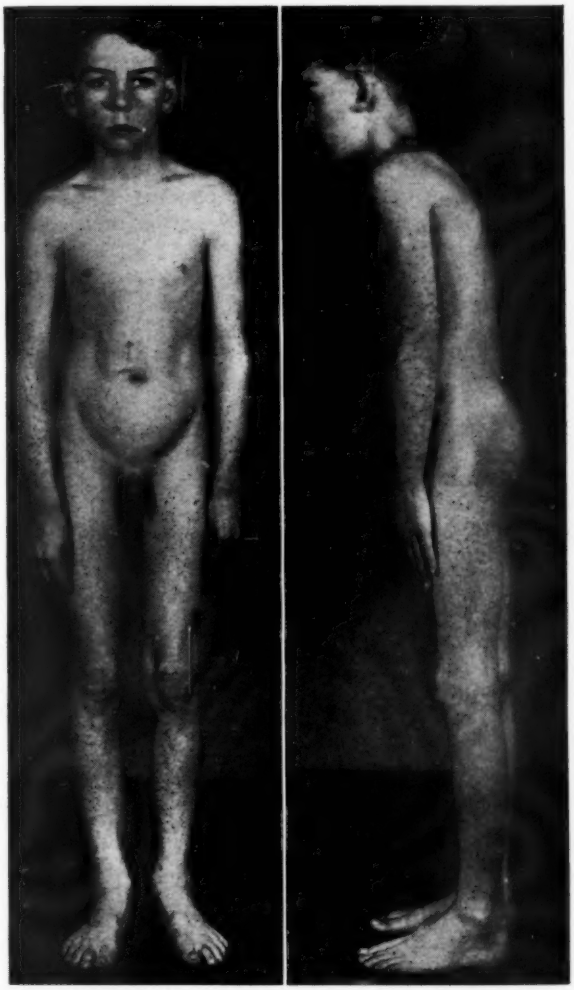

FIG. 2a and 2b.—The typical rash of anaphylactoid purpura.

blood-stained. The abdomen was diffusely tender and there was increased guarding of the left upper rectus. More purpura appeared and his urine contained numerous red cells. Fluid and ' anthisan,' mg. 300 daily, were given intravenously. Continuous gastric suction was employed and a quantity of mucopus aspirated.

The blood examination findings are summarized in Table 2.

On February 1, a non-herpetic stomatitis appeared, which was similar to that seen previously. The patient had profuse melaena, but his pain diminished and the rash faded. On February 4 a barium meal showed considerable jejunitis, but there was no obstruction. Oral feeding was started and the patient was given anthisan, mg. 500, daily. He continued to improve. Five days later a fresh crop of purpura appeared on feet and hands and after a further two days he again had abdominal pain, which quickly became severe. He vomited forcibly and intravenous fluid was again necessary. The anthisan was stopped, and penicillin, 120,000 units, was given six-hourly. The stomatitis again appeared, but was less pronounced. By February 17 he was again convalescent. On February 21 another crop of purpura appeared and became extensive the next day. One day later (February 23) he had diffuse abdominal pain in the evening and later passed a large quantity of fresh blood per rectum. He vomited once, but did not look ill. Melaena persisted in diminishing quantities for three days. By March 2 he was much improved and was allowed out of bed, but a week later had a slight attack of abdominal pain and two vomits, one of which contained a little blood. No rash appeared until March 14, when a few purpuric spots were noted, but these quickly faded. On March 31, a barium meal still showed some jejunitis. The patient was discharged to a convalescent home, and up to October, 1949, has had no relapse.

The original findings at operation, together with the subsequent demonstration of jejunitis radiologically, make it certain that the abdominal symptoms throughout were caused by acute ' regional enteritis.' It is interesting to speculate whether the changing symptomatology from sudden acute high obstruction to the later colic with melaena represents a different localization of the lesion. The child's condition during the second attack was certainly severe enough to have indicated immediate operation had the diagnosis not been suggested by the previous admission.

No focal sepsis was apparent and no streptococci were isolated from the throat.

The stomatitis was seen altogether on three occasions, although penicillin was given once only. Initially, a possible cause was the dehydration and marked sordes, but this could not have applied to later attacks when hydration was adequately controlled throughout. It remains a possibility that the stomatitis was part of the systemic disorder.

Capillary resistance was estimated on several occasions by direct suction using a 1 in. diameter cup for 30 seconds. Petechiae were readily produced in all the stained areas of the skin, indicating some residual capillary damage in these areas. The resistance elsewhere was slightly below normal and, curiously enough, showed no significant alteration when the anthisan was given or when relapses occurred. Parrot (1942) had previously reported a change in capillary resistance when antihistamins were given, but it is probable that the technique was not applied accurately enough in this case to determine any slight difference.

Case 2. H.C., a boy, aged 4¾ years, was admitted on December 23, 1947, with a history of vague ill-health for the previous two months. Two weeks before admission, he had had severe mid-abdominal colicky pain which recurred several times each day and gradually became more severe. His appetite was quite good and his bowels regular until three days before admission when they were constipated. For the last three days he had vomited all food, but had retained a little water. During the last week before admission a number of hard, purple spots had been noted on the buttocks, but no other rash was apparent.

CONDITION ON ADMISSION. The child was dehydrated and tired, but not acutely toxic. There was tenderness and rigidity in the right iliac fossa. A tender mass was palpable in the same place per rectum, and a diagnosis of appendix abscess was made.

Just before operation some small purpuric spots were noted on the penis, but in view of the definite abdominal findings operation was not delayed.

OPERATION FINDINGS. The abdomen was opened through a gridiron incision and a very large quantity of clear fluid escaped. Some coils of small intestine presented at the wound and one coil about 4 in. long and 18 in. proximal to the ileocaecal valve was bright scarlet in colour, but did not appear to be thickened.

TABLE 2

ANALYSIS OF BLOOD INVESTIGATIONS IN CASE 1

Date	Hb. (% Sahli)	White Blood Count	Platelets	Bleeding Time (minutes)	Clotting Time	B.S.R.
Jan. 1, 1949	95	9,000	Abundant	Normal	Normal	24
Feb. 2, 1949		8,600	230,000	2	3	20
Feb. 23, 1949	80	9,000				
Mar. 12, 1949						13

The mesentery of the small intestine proximal to this loop was oedematous. There were a few enlarged mesenteric glands. Appendicectomy was performed and the appendix found to be turgid and thick-walled. When it was opened the mucosa was oedematous and there were several submucous haemorrhages. Histological examination was not performed.

PROGRESS. On December 27 a purpuric rash appeared on the dorsum of both feet extending to about 2 in. above the ankles. A few small spots were noted on the hands. The rash became more widespread next day, but then began to fade. The appearance and distribution were characteristic of anaphylactoid purpura. On the evening of December 29 the child passed two dark stools, giving a strongly positive benzidine reaction. Two days later a further rash appeared, more widespread than before, and slight oedema of the feet was noted. By January 5, 1948, the rash had faded almost completely, but the child complained of severe abdominal pain during the night. Abdominal examination showed no abnormality. On January 6 there was a further outbreak of purpura, now involving the hands, feet, and buttocks extensively.

The temperature remained normal, but the child became gradually weaker and apathetic. He was placed on a milk diet, with the addition of vitamin C, mg. 100 daily, halibut oil, minims 20 daily, and vitamin B_1 mg. 5, three times a day. The oedema increased.

On January 10 a further rash appeared, now extending to the upper arms and shoulders and up the thighs. There was some colicky pain, but no further melaena. Oedema of the feet disappeared. On January 19 he was given a small transfusion, and following this, there was an increase in the number of red cells in the urine, and for several days he had gross haematuria. He complained of abdominal pain on January 25 and, next day, there was a fresh, profuse outbreak of purpura. As an index of his poor condition, the abdominal wound healed very slowly and there was an excess of unhealed granulation tissue, and later a small incision hernia. By February 17 the child was eating well and taking a good mixed diet. He gained weight during the last few weeks, and when discharged weighed 37 lb., a gain of 5 lb. since admission.

The child's condition on discharge was good, though there were still a few red cells in the urine. There was, however, little albumen, and for the three weeks before discharge, the urine had shown only slight deviation from normal. No casts were ever seen, and hypertension was absent throughout.

LABORATORY INVESTIGATIONS. Blood counts on Dec. 27, 1947, showed W.B.C., 12,000 c.mm., platelets abundant. Jan. 5, 1948: W.B.C., 8,400 c.mm., platelets abundant. Hess test negative. Clotting time 4 mins. Bleeding time 1½ mins. Jan. 14, 1948: Hb. 54%; W.B.C., 8,000; prothrombin index, 75% of normal.

URINE. Analysis on Jan. 14 showed numerous R.B.C.s; albumen 2 g./litre. Feb. 15: numerous R.B.C.s; trace of albumen. Mar. 6: occasional R.B.C.s; no albumen. May 5: no albumen. Addis count, 300,000 R.B.C.s in 12 hours.

The Mantoux test on Dec. 27, 1947, was 1/10,000 negative; Feb. 15, 1948, 1/10,000 positive; March 2, 1948, 1/10,000 positive.

On Jan. 6 a throat swab showed pneumococci. From Mar. 2 to 5 gastric washings were taken, but no tubercle bacilli were seen.

On Jan. 6 serum proteins were 3·54% (2·5% albumen; 1·04% globulin); Jan. 14, 4·4%; Feb. 6, 5·76%.

The post-operative hypoproteinaemia could not be explained in terms of the patient's previous diet. Vaughan, Thomson, and Dyson (1946) showed that the plasma protein level may fall post-operatively or after severe injury. It has been suggested (Croft and Peters, 1945) that this may be related to the need of particular amino-acids, especially methionine, for tissue repair, which are not readily available from the diet and must be provided by breakdown of tissue protein. In this respect, the unusual granulation tissue and subsequent development of a small incisional hernia are of interest. The oedema of the legs may have resulted from the low plasma proteins, as these were probably not estimated at their lowest level.

The interpretation of the positive Mantoux is difficult. Gairdner (1948) has pointed out that there is an unusual sensitivity to intradermal injection in this condition, and unfortunately no control test was performed. In the absence of collateral evidence of tuberculosis, a final opinion is impossible.

Case 3. J.H., a boy, aged 8 years, was admitted on October 7, 1948. He had complained of earache for three weeks before admission and appeared to be deaf. Similar attacks had occurred in the past and resolved without special treatment. During the last seven days his appetite had been poor and he had vomited several times in the last three days. He was sent home from school three days before admission with a diagnosis of tonsillitis and otitis. On the same day the mother noticed that his face was rather puffy. On the day before admission, the urine was dark red.

CONDITION ON ADMISSION. The patient was a well-grown boy, drowsy and uncooperative. His temperature was 102° F., and his skin was pale. He was deaf and there was a purulent discharge from both ears. His face was puffy and there was pitting oedema over the legs and sacrum. A widespread petechial rash was present on the extensor aspect of the limbs. The throat was red, but no pus was seen on the tonsils, which were of normal size. Blood pressure was 140/95. There was gross haematuria and, on microscopy, blood casts were seen.

PROGRESS. He was given penicillin and placed on a fluid diet. No further rash appeared, and the temperature became normal by the fourth day. At this time the blood pressure had fallen to 110/75 and his oedema was decreasing.

By November 5, 1948, he had improved considerably and was alert and cheerful. A short relapse followed a mild respiratory infection on November 19. Five days later he vomited in the afternoon and some inflammation of the throat was noted. Next day he vomited twice in the morning and later complained of central abdominal pain. His tongue was furred and he had diffuse superficial tenderness of the abdomen. Temperature and

pulse were normal. In the evening the pain became severe and he was extremely restless, sitting forward and moaning with discomfort. The abdomen was extremely tender and deep palpation was resisted, though there was no rigidity. The tenderness was difficult to localize, but, if anything, was most marked in the right iliac fossa. Rectal examination showed tenderness on the right side. Peritonitis was diagnosed and a laparotomy performed.

OPERATION FINDINGS. A right gridiron incision was made and a large quantity of blood-stained fluid escaped. The appendix and lower ileum were normal. A right upper paramedian incision was then made and the omentum was found to be lying on the left side. When this was moved several coils of bright scarlet intestine were seen. The area involved extended from the duodeno-jejunal flexure along the jejunum for 16 in. The bowel was grossly oedematous, and of such a brilliant colour that the blood in it must have been nearly fully oxygenated. The duodenum and stomach were normal. It was decided not to perform a short circuit, and the abdomen was closed. An intravenous drip was put up and continuous gastric suction employed.

POST-OPERATIVE COURSE. A course of penicillin was started immediately after operation in a dose of 5,000,000 units daily. The child was able to take fluids by mouth after five days, and the drip was then stopped.

On the tenth day, after the stitches had been removed, the suture line gave way and a re-suture was necessary. Opportunity was taken to inspect the bowel, which appeared grossly normal.

During the next few days the child occasionally complained of severe colicky pain. It was thought that this might be caused by adhesions. On December 26 he had severe abdominal pain and vomited three times. He was placed on a fluid diet and given an injection of heroin. A radiograph of the abdomen was normal. The pain lasted altogether some 36 hours, and during this time the haematuria increased until on December 29, 1948, he passed heavily blood-stained urine. No further purpura was noted. A few days later he seemed well and wanted to get out of bed. The gross haematuria persisted for some three weeks. The B.S.R. remained raised, but because of the child's well-being, it was decided to send him to a convalescent home. While there he contracted chickenpox, which passed uneventfully, and was not associated with any change in the urine.

LABORATORY INVESTIGATIONS. On Oct. 7, 1948, gross haematuria; Nov. 9., Addis count 2,000,000 R.B.C. in 12 hours; Nov. 23, Addis count 10,000,000 R.B.C. in 12 hours; Dec. 26, occasional R.B.C.; trace of albumen; Dec. 29, gross haematuria; April 4, 1949, trace of albumen; occasional R.B.C. A further Addis count was not performed.

Blood counts on Oct. 7, 1948, Hb. 76% (Sahli); W.B.C., 13,000. Platelets abundant. Bleeding and clotting times normal.

Mantoux test on Oct. 7, 1948, 1/10,000 negative.

Jones and Moore (1946) have reviewed the association of purpura with rheumatic fever and acute nephritis. While admitting that cutaneous erythemas of the *E. multiforme* type may occur in rheumatic fever, they consider true purpura uncommon, probably occurring in less than 1% of cases. They quote Fishberg to show that purpura is equally rare in nephritis. The common relapse of abdominal pain and haematuria in this child suggests a common aetiology, and it is likely that the original purpura belonged to the same syndrome. No other evidence is available to make a distinction from acute nephritis, and without the jejunitis no doubts would have been raised. The association of enteritis with nephritis has usually been in the chronic state and is widely reported under the title ' uraemic enteritis.' The child was certainly not uraemic, and it is debatable whether some cases of uraemic enteritis are not, in fact, vascular in origin.

A definite diagnosis would depend on an accurate distinction between acute nephritis and anaphylactoid purpura. Gairdner (1948) produces evidence to show that the distinction is largely artificial, although the extremes present characteristic pictures.

Case 4. E.W., a girl, aged 10 years, was admitted on October 8, 1948. Eight days before admission to hospital, she complained of epigastric pain and vomited several times. On one occasion, the vomit was blood-stained. The pain and vomiting persisted for three days and then subsided, to return two days before admission. On the night before she was admitted she vomited some bright red blood. Three days before admission she had complained of stiffness and pain in both knees, and the mother thought that they had been slightly swollen. A short time before this illness began there had been a transient, painless swelling of the right ankle. There was no history of recent infection.

CONDITION ON ADMISSION. The child was flushed and tired, with a temperature of 99·2° F. The tonsils were red and large, with a yellow exudate. There was an angular stomatitis and a generalized rash, having the appearance of small papules. There was no evidence of joint swelling.

PROGRESS. Penicillin, 50,000 units six-hourly, was given and the child appeared to improve. The rash quickly faded. Three days later, the temperature was normal and the throat healthy, but the child was restless and vomited several times. There was no complaint of abdominal pain. On October 14, 1948, a fresh rash appeared, consisting of purpuric spots over the buttocks and thighs, having the characteristics of the Henoch-Schönlein exanthem. Four days later she complained of colicky abdominal pain and was constipated. She was drowsy and her appetite poor. On October 21 a profuse purpuric rash appeared. She complained of severe abdominal pain and vomited several times. The abdomen was distended and slightly tender on the right side. After a time this subsided, and the next day the stools were loose, but not blood-stained.

The abdomen became distended during the next two days. A radiograph showed numerous fluid levels suggesting intestinal obstruction. She continued, however, to have frequent offensive stools. After three days the pain ceased, but the stools were not normal until October 30. No distension of the abdomen was then noticed.

On November 4 a barium meal showed no abnormality, and a fortnight later she was eating well, gaining weight, and free from purpura.

Tonsillectomy was later considered advisable, and to cover the operation on December 6 procaine penicillin, 1 ml. daily, was given. The urine again became smoky after the operation, but a week later there was only a trace of albumen and an occasional red cell.

She was discharged home on February 4, 1949, when the urine was clear, but the B.S.R. was still 30 mm. in 1 hour (micro-method).

LABORATORY INVESTIGATIONS. Urine analysis on Oct. 8, 1948, showed numerous R.B.C.s and heavy precipitate of albumen. Similar results were observed on Oct. 12 and Nov. 1. On Dec. 6 there was gross haematuria. On Feb. 4, 1949 there was no albumen, nor R.B.C.s. An Addis count was not performed.

Blood count on Oct. 8, 1948. Hb. 80% (Sahli); W.B.C. 12,000. Hess test negative. On Oct. 12, bleeding time was 2½ mins.; clotting time 4 mins.; platelets abundant.

A chest radiograph on Oct. 8, 1948, showed enlarged left hilar glands and infiltration at the left apex. A Mantoux test on the same day was positive 1/1,000.

A throat swab on Oct. 10, 1948, showed a slight growth of haemolytic streptococci.

The abdominal symptoms are of interest here in that radiographs showed a picture highly suggestive of paralytic ileus at a time when diarrhoea was still present. Brynjulfsen (1948) has reported this paradox in his cases of acute jejunitis and it may well be related to a widespread disturbance of normal peristalsis.

It will be noted that she was probably passing through her primary tuberculous infection at this time (cf. Case 2) and that although there was tonsillar sepsis on admission, few haemolytic streptococci were grown.

Case 5. D.M., a boy aged 8½ years, had previously been admitted to a medical ward and diagnosed as anaphylactoid purpura. That attack was complicated by severe abdominal pain with melaena, but he recovered after several weeks and was discharged home. Six months later, although he had recently been well, he had sudden acute mid-abdominal pain. This became colicky, and he vomited several times and quickly looked ill. He passed several blood-stained motions, but for a few hours before admission the bowels had not moved. Examination showed an ill child with a purpuric rash on the legs characteristic of anaphylactoid purpura. A large tumour was palpable in the left iliac fossa and the diagnosis of intussusception was made.

OPERATION FINDINGS. There was some clear fluid in the peritoneal cavity and a colic intussusception was discovered. The bowel was not unduly haemorrhagic and no explanation could be found for the profuse melaena. Operation was successful and the post-operative course was uneventful. No further purpura occurred and there was no haematuria.

Discussion

The intestinal lesion in Cases 1, 2, and 3 were essentially similar. In each, the segment of bowel affected was sharply separated from normal tissue. The mesentery and bowel were oedematous and of a curiously intense scarlet colour. There was no suggestion of such discoloration of the blood as might have been expected had there been interstitial bleeding. Despite the resemblance to an acute inflammatory erythema, the process did not spread to adjacent coils of gut. On each occasion a descriptive diagnosis of acute regional enteritis was made and only the later developments raised doubt as to the true diagnosis. In Case 4 a similar, though less severe, clinical course was accompanied by evidence of disordered peristalsis. In Case 5 this peristaltic disturbance seems to have induced true intussusception.

These five cases did not appear explicable in terms of mucosal purpura. The absence of any pigmentation of the tissues, together with doubts about the existence of any haemorrhagic tendency in this disease, further suggested that localized bleeding into the gut wall was not of primary importance. Nevertheless, the common recurrence of purpura and intestinal symptoms strongly suggests that the same vascular lesion is operative.

The Vascular Lesion. The rash normally consists of blood-stained macules, though simple oedema may occur. Occasional lesions become gangrenous resembling those seen in purpura necrotica (Sheldon, 1947). In either case, their local distribution may be occasioned by trivial injury. Histological changes are restricted to the small vessels of the corium which are surrounded by a cuff of white cells (Gairdner, 1948). Tissue eosinophilia is sufficiently frequent to suggest a local anaphylactic reaction. There is some swelling of the collagen fibres, but no fragmentation and there are no areas of fibrinoid degeneration. Capillary microscopy during the appearance of the rash shows that the exudate comes from the end of the pre-capillary arteriole and that the capillary wall remains intact (Humble, 1949). Capillary fragility tests have been equivocal. Davis (1948) found 25% positive in his series, but gives insufficient data for a proper appraisal of his results. Limited personal experience with a direct suction method has shown a marked difference between the capillaries of the purpuric areas and the surrounding skin which persists until the rash is barely visible. For this reason the true resistance is difficult to estimate and low readings may be obtained because sufficient care is not taken to map the distribution of the fading lesions.

The renal lesion has been taken to indicate a degree of capillary damage. It is chiefly remarkable among the complications of this disease in that it may progress to a chronic stage indistinguishable throughout its course from Type I nephritis (Ellis,

1949). Any process, however, which leads to persistent glomerular haemorrhage might be expected to proceed to crescent formation and later capsular fibrosis. Indeed, it has recently been suggested that pre-capillary vasospasm is the immediate cause of glomerular haemorrhage in acute nephritis (Ellis, 1949).

Although abdominal symptoms are seen in over 50% of cases admitted to paediatric units, pathological details are lacking. The colic, when severe, may suggest intussusception and operation has usually been advised to eliminate this possibility. Several authors have described the appearance of the bowel (Bailey, 1930; Mailer, 1938; Barnes and Duncan, 1941) and all have agreed that haemorrhagic extravasation into the intestinal wall is present. Bailey (1930) states that the appearance might be reproduced by the injection of fresh blood under the serosal surface and so emphasizes the absence of tissue-staining by bile pigments.

The lower ileum is usually involved (Gairdner, 1948) though both stomach and jejunum may be affected (Bailey, 1930; Silbermann, 1890). Local ulceration of the mucosa associated with fibrinoid necrosis of the small vessels has been reported (Wassilieff, 1937), but most accounts merely reveal localized sub-mucosal haemorrhage, even though previous operation had shown acute engorgement (Sturtevant and Graef, 1933).

Anaphylactoid purpura may be described as a diffuse arteriolitis, but it is impossible to explain the abdominal lesion simply in terms of damage to the arterioles. Such damage has only been noted in the submucosa, the larger vessels appearing normal. On the analogy of the intestinal lesions found in malignant hypertension and in periarteritis nodosa which remain localized although the underlying vascular change is widespread, it is suggested that vasospasm is a complication of the initial vascular damage. It is significant that a similar form of regional enteritis may complicate symmetrical cortical necrosis of the kidney (Dunn and Montgomery, 1941), in which primary vasospasm is generally accepted as the cause of the renal lesion, and Campbell and Henderson (1949) have shown that both renal and intestinal lesions may occur simultaneously.

The appearance at operation of acute regional enteritis is not, however, entirely explicable by local vasospasm. The bright red hyperaemic tissue indicates a fast blood-flow through dilated vessels, whereas in paralytic distension following spasm it might be expected that the blood-flow would be sluggish and that there would be extravasation of blood into the tissues. The intestinal lesion could best be explained by a submucosal shunt with intense local spasm diverting the greater part of the blood-flow to the outer layers of the bowel. A mechanism of this type has recently been demonstrated by Barclay and Bentley (1949) in the gastric mucosa, and it is at least possible that similar shunts may occur throughout the bowel. Such a mechanism provides an acceptable explanation of the intensity and transience of the symptoms. Irreparable damage would then depend on the degree of mucosal ischaemia and the consequent infection. Vascular disorders at the submucosal level may be expected to disturb the normal integration of the intrinsic nerve plexuses. It is probable that the abnormal peristalsis in Case 4 and the development of true intussusception in Case 5 are symptomatic of this disturbance.

Despite the generally accepted view that anaphylactoid reactions primarily affect capillary endothelium, it may be that in anaphylactoid purpura any capillary damage which occurs is conditioned by pre-capillary vasospasm and consequent anoxia.

Summary

The alimentary lesion in anaphylactoid purpura is described and five illustrative cases are reported in detail.

It is suggested that in anaphylactoid purpura local vasospasm is responsible for the segmented lesions in the bowel, such vasospasm being secondary to damage of the arterioles.

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STUDIES OF THE CEREBROSPINAL FLUID CIRCULATION IN TUBERCULOUS MENINGITIS IN CHILDREN

PART II. A REVIEW OF 100 PNEUMOENCEPHALOGRAMS

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Since the introduction by Dandy of the technique of ventriculography (1918) and encephalography (1919) their use has become an indispensable part of neurological investigations. No mention was made of their use in tuberculous meningitis until 1927 when Eckstein reported on the examination of 20 children suffering from this disease. He found varying degrees of hydrocephalus and presumed that this was inevitable in tuberculous meningitis. His view accorded with the usual necropsy findings and thereafter little further work was carried out until the advent of streptomycin. Since then many references have been made to air studies in this disease. Hydrocephalus was frequently found and its causes were analysed by Cairns (1949). In spite of the extensive work on various aspects of tuberculous meningitis treated with streptomycin, only two detailed reports were found on encephalography in presumably unselected groups of cases (Murano, 1948; Schönenberg, 1950).

Present Investigation

Material. This investigation began in September, 1948. At first air studies were only carried out for special reasons. The investigation was soon extended when increasing experience suggested that the procedures were safe and that more could be learnt by systematic and repeated examinations. Between January, 1949, and August, 1950, at least one pneumoencephalogram* has been performed on all but two patients treated for tuberculous meningitis. The two patients excluded were moribund on admission and died within a few days. No examinations were carried out in four other patients admitted in the latter half of 1948. Three of these died, and one recovered without any complications. With the exception of these six cases, the present series is consecutive and unselected. Five children treated at the same hospital but not under our own care were also investigated.

This study reports the results of the first 100 examinations† on 58 children aged between 5 months and 12 years. Tuberculous meningitis was bacteriologically confirmed in 57. The exception was a one-year-old tuberculin positive child of tuberculous parents, who showed the radiological appearances of a primary tuberculous lung complex. The cerebrospinal fluid was characteristic and after 22 months was still slightly abnormal, the child having recovered apart from a residual hemiparesis.

Objects of the Investigation. The long term objects of this investigation were: (1) a more complete understanding of the circulation of the cerebrospinal fluid in tuberculous meningitis; (2) the determination of the incidence and the sites of obstruction within the ventricular system and the subarachnoid cisterns; (3) the determination of the incidence, degree, permanency, and causes of hydrocephalus; (4) the establishment of criteria of prognosis on the basis of encephalographic findings; (5) the correlation of encephalographic patterns with subsequent physical and mental development; and (6) possibly the finding of definite criteria for the selection of suitable cases for treatment, and conversely, for the abandonment of treatment on humanitarian grounds.

Methods. All encephalograms were performed under rectal thiopentone anaesthesia (Lorber, 1950a). Air was injected by the lumbar route in all cases, except where spinal block necessitated the cisternal route. Approximately two-thirds to three-quarters of the fluid removed was replaced by air, 20 to 80 ml. being injected while the child was in the sitting position. An attempt was made to introduce air into the ventricles as well as the subarachnoid spaces by appropriate positioning of the head (Brain, 1947).

* This term will be used for both encephalograms and ventriculograms, unless otherwise stated.

† 89 encephalograms and 11 ventriculograms.

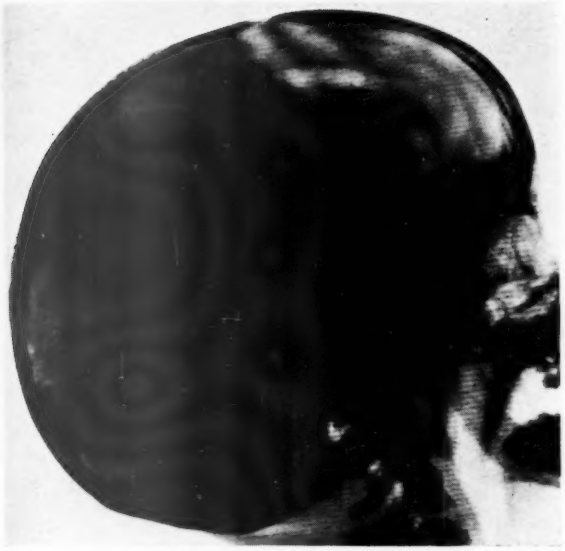
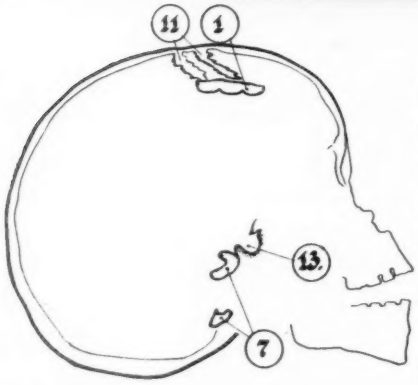


FIG. 1.



FIGS. 1 and 1a.—Encephalogram showing the upper level of the lateral ventricle (1) near the surface of the hemisphere, widened suture lines (11), and air collecting in the basal cisterns (7) behind the sella (13).

FIG. 1a.

Much information may be obtained by the injection of as little as 5 to 10 ml. of air, if the films are taken in the erect position. This method was employed by Flesch and Gefferth (1949) on a large number of cases. This volume of air can be injected after a routine therapeutic puncture without any preparation. This method was used only as an intermediate step in the present investigation. Figs. 1 and 1a illustrate the result of one such examination.

Encephalography was preferred to ventriculography because the former will usually, at the same time, outline the ventricular system as well as the subarachnoid space, and it is easier to detect blocks in any situation by that technique (Davidoff and Dyke, 1946a). Ventriculography was done if the ventricles failed to fill due to obstruction of the pathways, or if encephalography was contraindicated by papilloedema.

The whole procedure was carried out in the x-ray department. Pilot films were taken during the injection of air to guide the positioning of the head and the assessment of the volume of air to be injected. The final radiographs of the skull were taken in four standard positions: antero-posterior and lateral with the patient horizontal and erect respectively. Additional views were taken if the films suggested special features requiring elucidation.

The radiographs were interpreted by the standards of Caffey (1945) and Davidoff and Dyke (1946). An encephalogram was judged to be normal if the ventricular system filled well, showed no signs of dilatation, and if air was obviously present in the subarachnoid spaces (Figs. 2, 2a, and 3, 3a). Dilatation of the ventricles was diagnosed if the size of the ventricles exceeded the limits given by Davidoff and Dyke.

After-effects. These procedures were found to be safe. With one exception no serious after-effects were noted. One infant had been unconscious for three and a half months before ventriculography which disclosed extreme hydrocephalus (Fig. 4, 4a). He died within 24 hours of the examination. His death may have been accelerated.

Pneumoencephalography was well tolerated by most childeren, especially if they spent three hours in an oxygen tent following the examination. This procedure has been shown to hasten the absorption of the injected air (Fine, Frehling, and Starr, 1935; Kornreich, 1948; Schwab, Fine, and Mixter, 1937). The children had often no memory of the examination and were found sitting up and playing six or seven hours after it. Moderate headache and some vomiting for 24 hours was, however, fairly frequent. Air must be removed if symptoms of excessive pressure should supervene. The after-effects were proportionately milder when the volume of injected air was less. This was also noted by Davidoff and Dyke (1946b).

It has been suggested that pneumoencephalography may precipitate a relapse of the meningitis (MacCarthy and Mann, 1950). The probable fallacy of this statement was pointed out elsewhere (Lorber, 1950b). In none of the present series was there clinical or other evidence of relapse within two months of the examination. It is as well to remember, however, that the introduction of air may provoke a considerable cellular reaction even in patients whose cerebrospinal fluid was normal at the beginning of the injection. This pleocytosis may occasionally reach several thousand cells but will usually subside within eight days (Cestan and Riser, 1924; Eley and Vogt, 1932; Hermann, 1922; Kryspin-Exner, 1932; Merritt and Fremont-Smith, 1937; Schwab and von Storch, 1937; Thurzó and Nagy, 1923; and Tschugunoff, 1929). The increase in the cell count starts immediately after the injection of air. In one of the present series of cases separate examination of each 5 ml. specimen of fluid during the course of an encephalogram showed a tenfold increase in the cell count. A mere rise in cell count following pneumoencephalography should not be

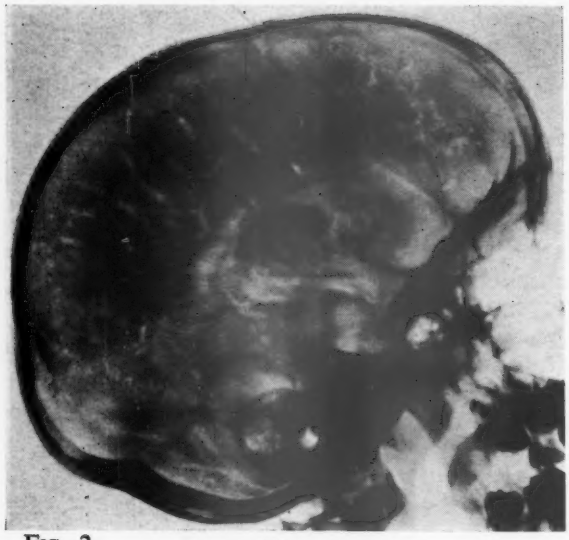
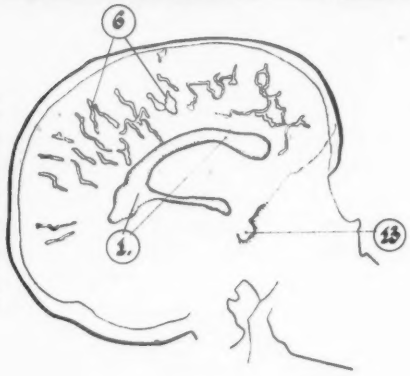


FIG. 2.



FIGS. 2 and 2a.—Normal encephalogram from a case of tuberculous meningitis 32 weeks after the beginning of treatment showing normal sized lateral ventricles (1), air in the subarachnoid space (6), and the sella (13).

FIG. 2a.

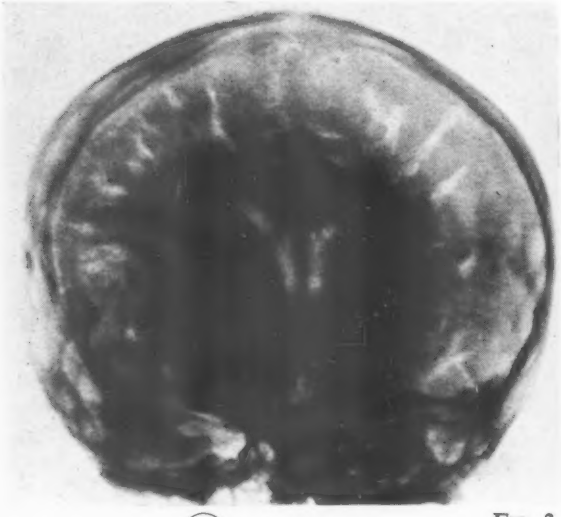
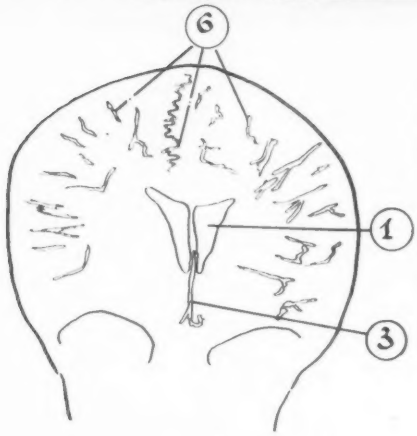


FIG. 3.



FIGS. 3 and 3a.—Normal encephalogram (AP) from a case of tuberculous meningitis after 22 weeks of treatment, showing normal sized lateral (1), and third ventricles (3), and air in the subarachnoid space (6).

FIG. 3a.

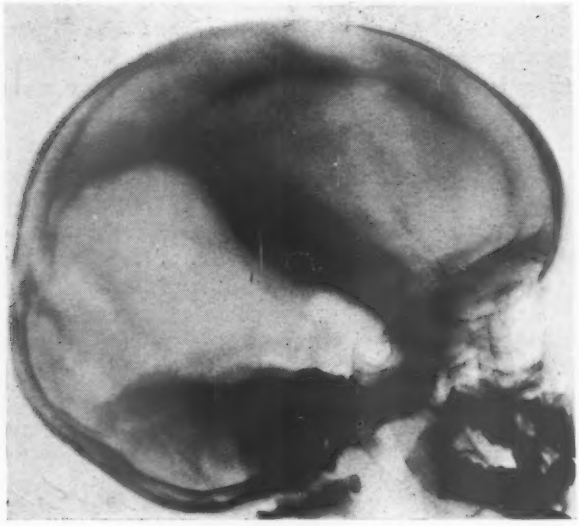


FIG. 4.

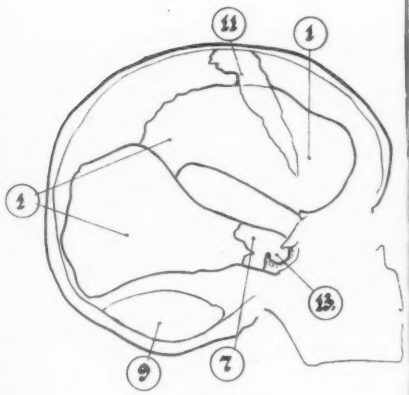


FIG. 4a.

FIGS. 4 and 4a.—Ventriculogram showing extreme dilatation of the lateral ventricles (1), gross widening of the sutures (11), and air trapped in the basal cisterns (7), behind the sella (13), and in the posterior fossa (9). The child died within 24 hours of the examination.

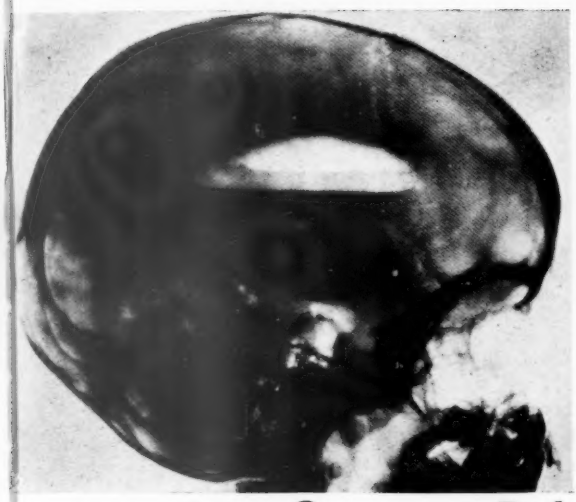


FIG. 5.

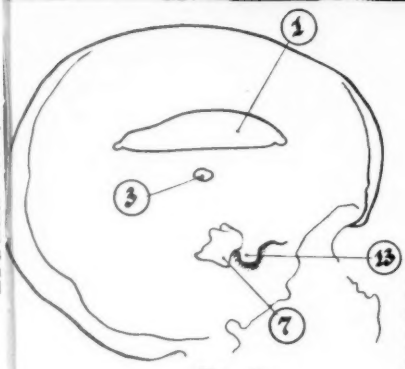


FIG. 5a.

FIGS. 5 and 5a.—Encephalogram showing block at the tentorial opening. The lateral ventricles (1) are dilated, there is air in the third ventricle (3), and a large collection of air in the distended basal cisterns (7) behind the sella (13). No subarachnoid air.

FIGS. 6 and 6a.—Lateral view of Figs. 12 and 12a, showing dilatation of all parts of the ventricular system: the lateral ventricles (1), foramen of Monro (2), third ventricles (3), Sylvian aqueduct (4), and fourth ventricle (5). The sutures are widened (11) and there is no subarachnoid air. Air distends the cisterna magna (9), but there is no bubble of air behind the sella (13), indicating obstruction in the basal cisterns.

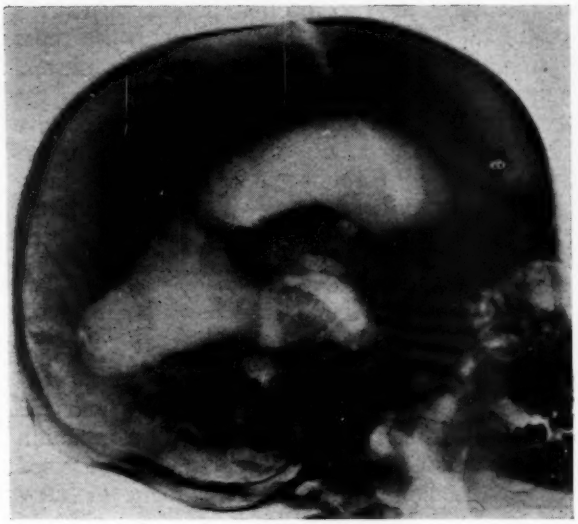


FIG. 6.

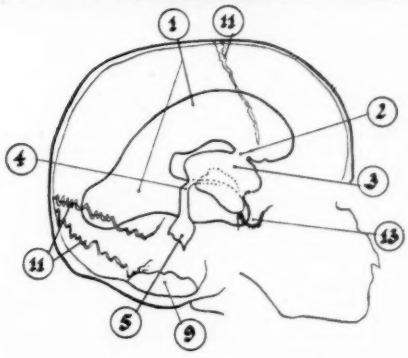


FIG. 6a.

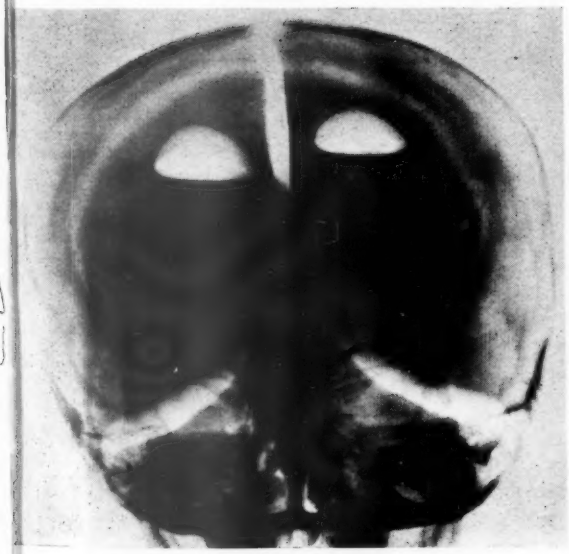


FIG. 7.

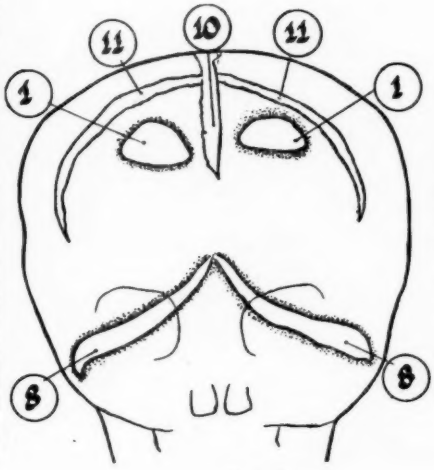


FIG. 7a.

FIGS. 7 and 7a.—Encephalogram (AP) showing probable block at the tentorial opening. The lateral ventricles (1) are grossly dilated, the suture lines (11) are widened. Subdural air is seen under the tentorium (8) and along the falx (10). No subarachnoid air.

taken therefore as an indication of relapse in the absence of other evidence.

Results. The results of the present investigation are discussed in two groups according to the radiological findings. In the first group are those children in whom the examination disclosed normal conditions, and in the second those in whom the appearances were abnormal. As six of a consecutive series of 64 cases were not investigated, the proportion of normal to abnormal findings is probably slightly distorted, because in five of the six omitted cases, the appearances would probably have been abnormal.

Group I: Children with Normal Radiological Appearances

Twenty-eight, or nearly half the children belonged to Group I. In 11 of them only one examination was carried out, and in eight of these was performed either late in the course of treatment or after treatment had been concluded, at an average of 33 weeks after the first streptomycin injection. All these children were in good clinical condition at that time.

The examinations were repeated two to four times in 17 of the 28 children whose initial encephalogram was normal. In 15 of these 17 the initial examination was carried out at an average of 2·3 weeks after the start of treatment when streptomycin had already had an opportunity to effect some improvement.

The subsequent examinations were carried out either for clinical reasons (unfavourable progress, convulsions, relapse) or to assess the condition

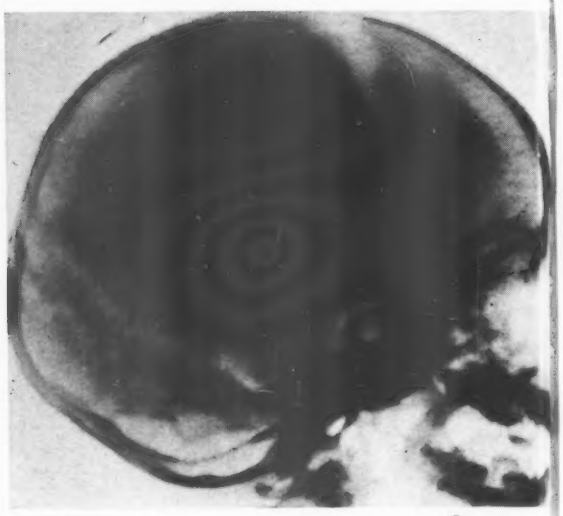
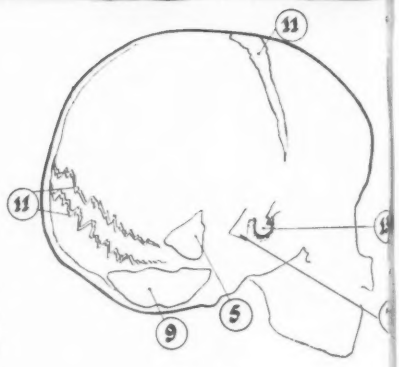


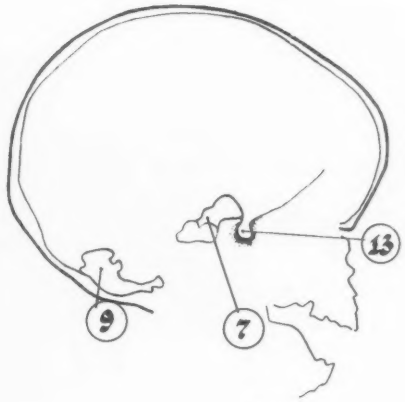
FIG. 8.



FIGS. 8 and 8a.—Encephalogram showing block at Sylvian aqueduct. The fourth ventricle (5) is dilated but no air penetrated beyond the beginning of the aqueduct. The suture lines are widened (11) suggesting hydrocephalus. Tentorial block is also present, because air is held up in the basal cisterns (7) behind the sella (13) and in the cisterna magna (9). There is no air in the subarachnoid spaces.

FIG. 8a.

FIG. 9.



FIGS. 9 and 9a.—Encephalo showing block at foramina i roof of the fourth ventricle. distends the basal cisterns behind the sella (13), and cisterna magna (9), but penetrated into the ventricl to the subarachnoid spac

FIG. 9a.

towards the end of the proposed course of treatment. In 11 children the appearances remained normal after an average interval of 18 weeks between the first and last examinations. In six other children pathological changes appeared at the second or a later examination. This leaves altogether 22 children with normal encephalographic appearances, in 18 of whom they were found between four and 14 months after the beginning of treatment. Hydrocephalus is thus by no means an essential pathological feature of tuberculous meningitis.

Group II: Children with Abnormal Radiological Appearances

There were 36 children in Group II, including the six in whom the first examination was normal, but in whom abnormalities were detected later. Three main abnormalities were seen: (1) the presence of one or more blocks in the cerebrospinal pathways; (2) absence of air in the subarachnoid space; and (3) hydrocephalus of various degrees. As the last two features are usually the result of the first, all three were often found together. In addition, some less common features (cyst formation, subdural air) were also noted.

Blocks. Blocks other than those within the spinal theca were seen in 30 of the 36 children and in two others their presence was not definitely excluded by ventriculography. In five children blocks were demonstrated at two sites, but in every one of the 30 cases with blocks one of these was situated either at the tentorial opening or in the basal cisterns. A block at the tentorial opening can be recognized in the lateral film by the collection of air in the distended cisterns behind the sella together with the absence of subarachnoid air (Smith, Vollum, and Cairns, 1948) and often by the collection of air under the tentorium (Figs. 5 and 5a). The encephalogram is similar when the block occludes the basal cisterns, except that the air is held further back, in the cisterna magna (Figs. 6 and 6a). In the anteroposterior film the normal filling of the lateral ventricles, with the absence of subarachnoid air and often the presence of a large collection of subdural air under the tentorium, is strong indirect evidence of a block at these sites, especially if the ventricles are already dilated (Figs. 7 and 7a.) The presence of air in the sulci over the hemispheres excludes the possibility of a block at the tentorial opening, irrespective of other suggestive features.

In two children the block occluded the Sylvian aqueduct. This is a rare condition in tuberculous meningitis. It was demonstrated by the failure of the ascending air to outline the ventricular system above the level of the distal end of the Sylvian aqueduct (Figs. 8 and 8a). At necropsy these blocks were verified by the finding of a small tuberculoma completely obstructing the aqueduct in each case. In three other cases the foramina in the roof of the fourth ventricle were obliterated, as shown by air distending the basal cisterns, but failing to enter the ventricles (Figs. 9 and 9a) having been injected by the lumbar route. These blocks were also verified at necropsy.

It is of great practical interest to know the time of onset of these blocks. Although it was found that they may occur at any stage of the disease and during treatment, it seems likely that in the large majority they were already present before treatment had started. As no encephalograms were performed in any of these children before treatment, this cannot be stated with certainty. In 17 of the 30 patients with blocks, however, the examination was carried out within a fortnight, and in 22 within five weeks of the beginning of the treatment, and the blocks were already present. In only six children was the appearance of blocks observed during the course of the treatment after a previously normal encephalogram. These were demonstrated between six and 53 weeks after intrathecal treatment had started and active infection was still present in all. When such a block appears it can often be recognized by the rapid deterioration in the child's condition.

CASE 1. A girl of 4½ years had been treated for tuberculous meningitis and her clinical condition had been favourable for eight months although the cerebrospinal fluid remained grossly abnormal and tubercle bacilli were found from time to time. Her progress was followed at intervals by repeated encephalograms, and three of these all showed normal appearances. She was bright, active, and interested during this time, playing like a normal child. In the thirty-sixth week she started vomiting, complained of headache, became drowsy, and within a week became unconscious. An air encephalogram now showed a block at the basal foramina, and penicillin assay (Lorber and Stewart, 1950) confirmed this finding. In spite of ventricular punctures she died within a fortnight. Necropsy confirmed the diagnosis.

Absence of Air in the Subarachnoid Space. Absence of air in the subarachnoid space was the second main abnormality noted. This may occasionally occur in normal persons without an obvious reason, but in this series good filling of the subarachnoid space was seen with remarkable regularity in children with otherwise normal encephalograms and its absence was regularly connected with or followed by other abnormalities. In three children the absence of subarachnoid air was the first abnormality noted and preceded the development of hydrocephalus. There were only four children in whom hydrocephalus was demonstrated in spite of the presence

of some subarachnoid air, and in one of them the hydrocephalus was unilateral.

Occasionally air may find its way into the subdural space after lumbar injection. Subdural air is not necessarily pathological, and its importance lies in the possibility of confusing it with air in the subarachnoid space. If mistaken for the latter, cortical atrophy or the absence of tentorial block may be incorrectly inferred. Subdural air does not occupy the sulci but occupies the whole surface of the brain and it is mobile, as shown when films are taken in various positions of the head (Figs. 10 and 10a, 11 and 11a). In anteroposterior projections taken in the upright position it may outline the longitudinal sinus (Figs. 11 and 11a) and often occupies the space along the falx and the under surface of the tentorium (Figs. 7 and 7a). More detailed observations regarding subdural air may be found in a study by Smith and Crothers (1950).

Hydrocephalus. Hydrocephalus is the third common abnormality (Figs. 6 and 6a, 12 and 12a). Its presence was demonstrated in 34 of the 36 children in this second group. In the other two ventricular filling was not obtained by encephalograms

TABLE 1

CLINICAL AND ENCEPHALOGRAPHIC FEATURES IN SIX CHILDREN WITH HYDROCEPHALUS

Case No.	Age on Admission (Years)	Sex	Condition at Beginning of Treatment	Pneumoencephalogram (weeks after beginning treatment)	Condition at Time of Encephalography	Result of Examination	Length of Follow-up (months)	Condition* on 30.9.50.
2	1½	M.	Coma	First: 7	Coma	Considerable hydrocephalus	26	Physically well. C.S.F. normal. Retarded (I.Q.=53).
				Second: 22	Recovered	No change		
3	5	F.	Coma	First: 2	Coma	Moderate hydrocephalus (Fig. 13)	17	Very well. C.S.F. normal. Optic atrophy. Vision (6/12:6/24). Fields restricted. (I.Q.=101.)
				Second: 7	Coma, spinal block	Increased hydrocephalus Cyst right frontal lobe (Fig. 14.)		
				Third: 17	Fully conscious Doing well, spinal block resolved	Same (Fig. 15.)		
4	1½	M.	Drowsy, apathetic	First: 5	Drowsy, irritable, wasting	Slight hydrocephalus	17	Well, C.S.F. normal. Hemiplegic, deaf, and grossly retarded. (I.Q.=below 30).
				Second: 21	Much brighter, recovering	Gross hydrocephalus. Cyst right frontal lobe		
5	3½	F.	Coma, hemiplegia	First: ½	Coma, hemiplegia	Slightly dilated ventricles No block	12	Very well. C.S.F. normal. Residual hemiplegia. (I.Q.=77.)
				Second: 5	Drowsy, irritable, hemiplegia	Increased hydrocephalus tentorial block		
				Third: 7	Same	Considerable hydrocephalus		
				Fourth: 17	Very well, hemiplegia	Same		
6	5	F.	Acutely ill, fully conscious	First: 1	Extremely ill, bulbar palsy	Moderate hydrocephalus	8½	Very well. C.S.F. slightly abnormal. Still treated. (I.Q.=100+.)
				Second: 22	Recovering, satisfactory progress	Much increased hydrocephalus		
7	2½	M.	Coma	First: ½	Coma	Moderate hydrocephalus	8½	Well. C.S.F. normal. Rapid mental improvement continuing. (I.Q.=61.)
				Second: 9	Conscious but blind	Gross hydrocephalus, especially of posterior horns		
				Third: 27	Recovered, and has good vision	Regression of hydrocephalus to original size		

* All children alive on 20.1.51. Minimum follow-up 12 months.

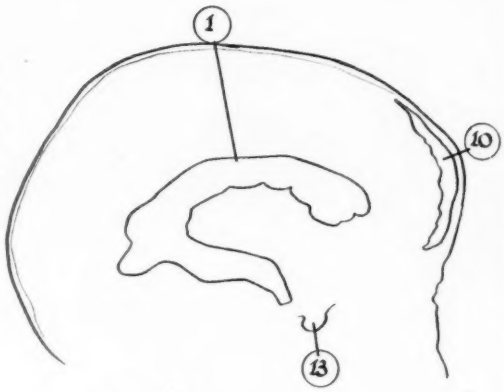
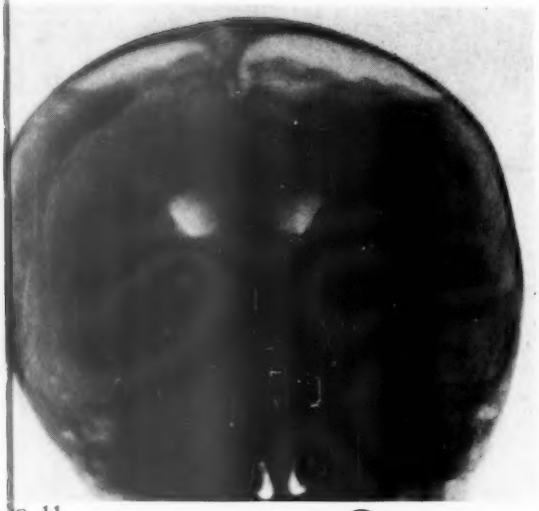


FIG. 10a.

IGS. 10 and 0a.—Lateral ew taken with row up, showing lateral ntricles (1), e sella (13), nd a pocket of ubdural air (10) overing the frontal cortex.

FIG. 10.



IG. 11.

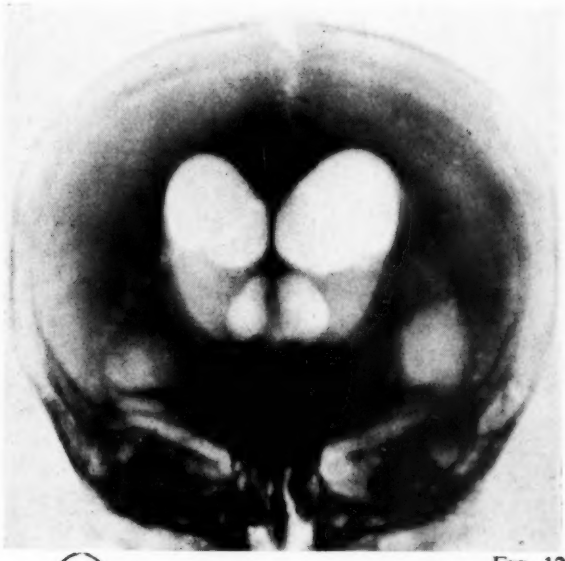


FIG. 12.

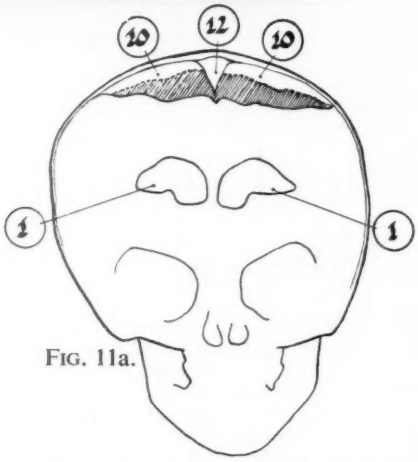


FIG. 11a.

S. 11 and 11a.—Antero-posterior view, showing the lateral tricles (1), air in the subdural space (10) outlining the superior gitudinal sinus (12). The shaded area is the surface of the brain. There is no air in the subarachnoid space.

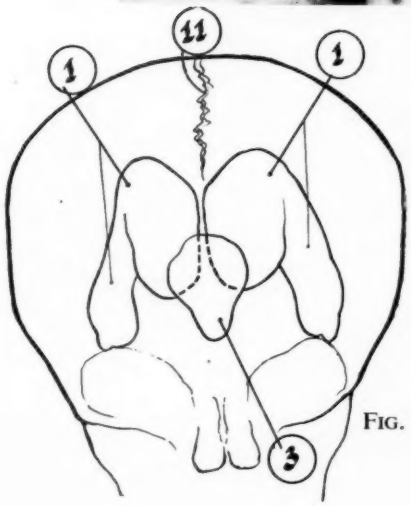


FIG. 12a.

FIGS. 12 and 12a.—Antero-posterior view of Fig. 6. There is considerable dilatation of the lateral (1) and third ventricles (3), absence of air in the subarachnoid space and widening of the sutures.

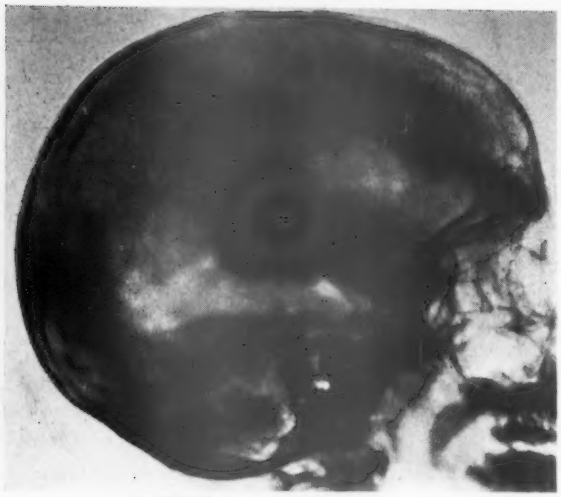


FIG. 13.

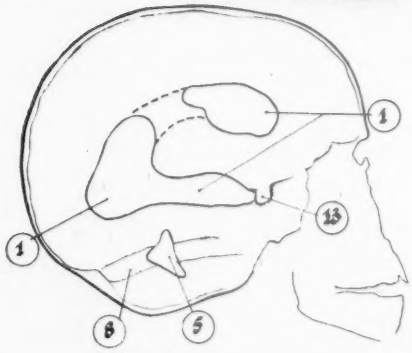


FIG. 13a.

FIGS. 13 and 13a.—First encephalogram (Case 3) two weeks after beginning of treatment showing moderate dilatation of the lateral ventricles (1) but not of the fourth ventricle (5). Air is held up under the tentorium (8) and there is none in the subarachnoid spaces. The sella is shown (13).

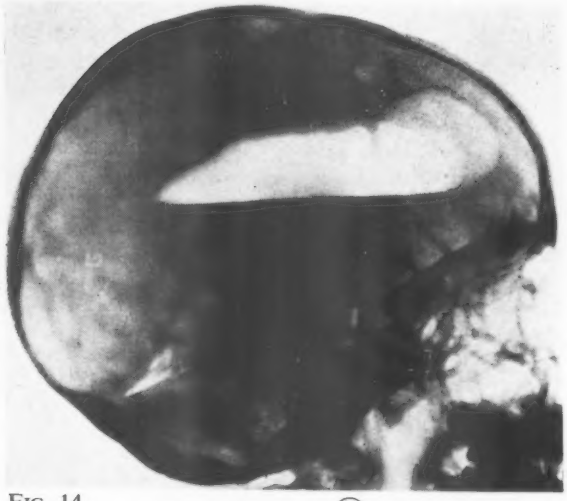


FIG. 14.

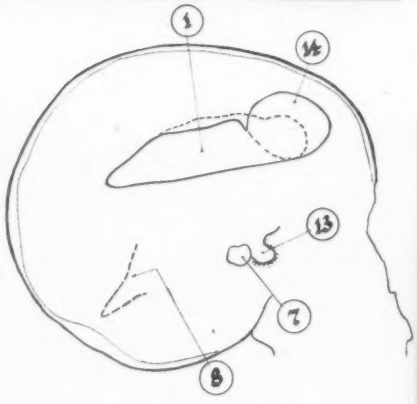


FIG. 14a.

FIGS. 14 and 14a.—Ventriculogram (Case 3) seven weeks after beginning of treatment, showing gross increase in the size of the lateral ventricles (1) since the previous examination. Air is still held up under the tentorium (8) and also in the basal cisterns (7) behind the sella (13). There is a large cyst (14) in the right frontal lobe, communicating with the ventricle.

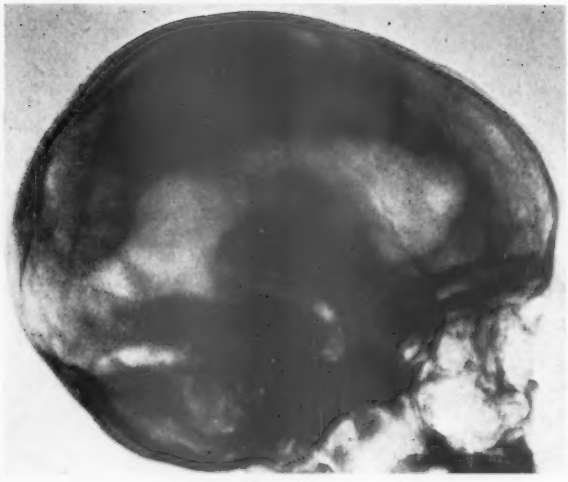


FIG. 15.

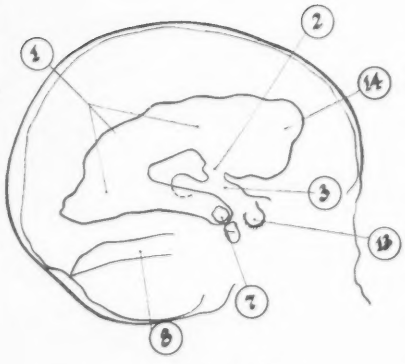


FIG. 15a.

FIGS. 15 and 15a.—Final encephalogram (recumbent position) 17 weeks after admission of Case 3 showing at least as great dilatation of the lateral ventricles (1) as before. The foramen of Monro (2) and the third ventricle (3) are also demonstrated. Air is still present under the tentorium (8) and in the basal cisterns (7) behind the sella (13). The right frontal lobe cyst (14) is still present. There is no air in the subarachnoid space.

FIGS. 16 and 16a.—Encephalogram of Case 7, at the time of blindness showing gross dilatation of the lateral ventricles (1) but especially that of the posterior horns. Air is collecting under the tentorium (8) and in the cisterna magna, but none behind the sella (13). There is no air in the subarachnoid space.

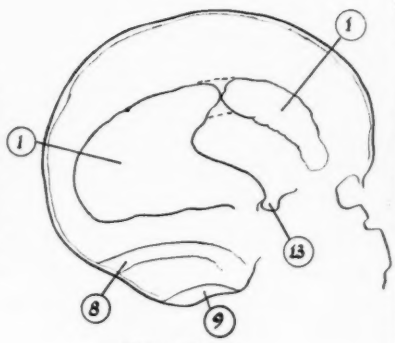


FIG. 16a.

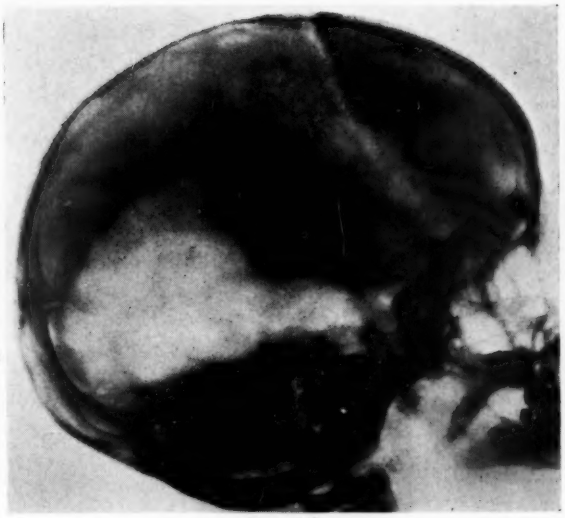


FIG. 16.

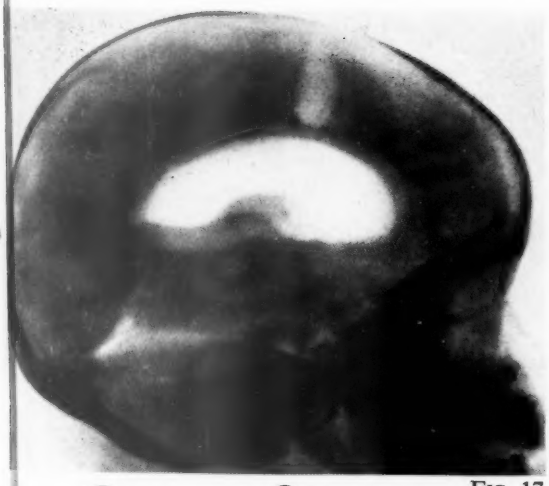


FIG. 17.

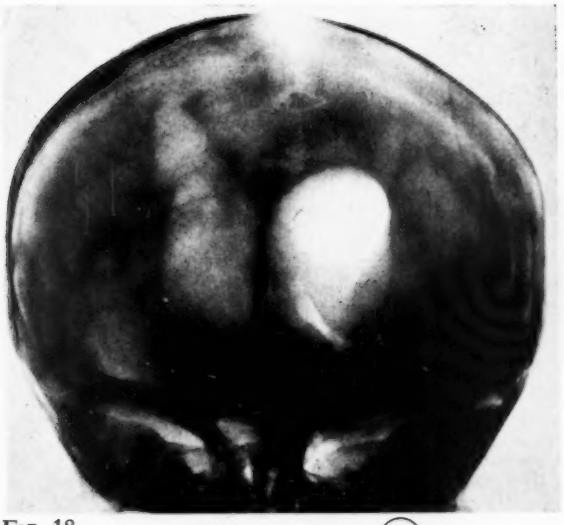


FIG. 18.

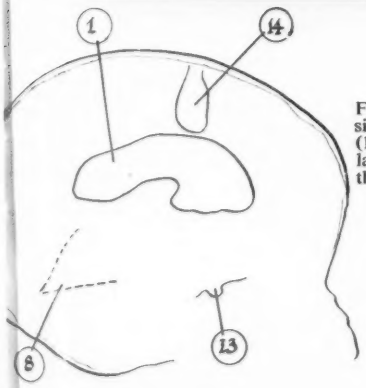


FIG. 17a.

FIGS. 17 and 17a.—Traumatic cyst at the site of a ventricular puncture track (14). There is considerable dilatation of the lateral ventricles (1), and air collects under the tentorium (8). There is no air in the subarachnoid space.

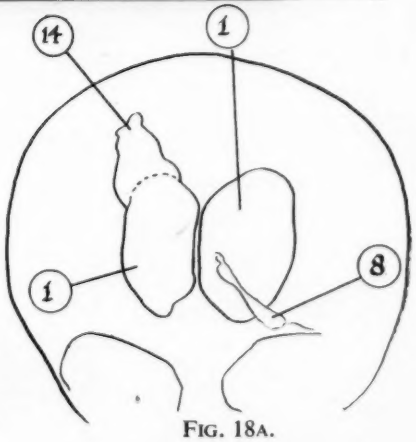


FIG. 18A.

FIGS. 18 and 18a.—Asymmetrical hydrocephalus and traumatic cyst (14) in the left hemisphere following ventricular puncture. The right lateral ventricle (1) is larger. Hemiplegia was present on the opposite side. There is subdural air under the tentorium (8).

due to blocking of the foramina in the roof of the fourth ventricle. Ventriculography was not performed, but at necropsy ventricular dilatation was found in both cases and the site of the block was confirmed.

The hydrocephalus was symmetrical in all but three cases although slight differences in size between the two lateral ventricles were frequently seen. A slight tilt or rotation of the head was enough to cause such apparent asymmetry. In three children, however, one lateral ventricle was definitely larger than the other (Fig. 18 and 18a): all had hemiplegia on the opposite side of the body.

The degree of hydrocephalus varied from slight (Figs. 11 and 11a) to extreme (Figs. 4 and 4a), according to the timing of the examination. The examination was not repeated in nine children whose clinical progress was poor and in whom considerable hydrocephalus was demonstrated on the first occasion. It is likely that hydrocephalus increased further in size up to the time of their death. This belief is based on the observation of 13 other children who are either dead or whose condition makes recovery extremely unlikely and in whom repeated examinations showed a progressive increase in the degree of hydrocephalus.

It is of particular importance to observe the progress of hydrocephalus in those children who made an apparent recovery or are making such good progress that their recovery is likely. There are six such children in this series whose progress was watched by repeated air studies. Details are presented in Table 1, but some addition is necessary in two cases.

CASE 3. The spontaneous formation of a cerebral cyst in the right frontal lobe communicating with the lateral ventricle was demonstrated at the second examination, when the first ventricular puncture was performed. The cyst was in front of the needle's track (Fig. 14 and 14a). Soon after this examination the child's sensorium began to clear and some four weeks later she was fully conscious. Since then her progress has been excellent and she was very well when the last encephalogram was performed. Further examinations were not justifiable and therefore the present size of her ventricles is not known with certainty, but it seems that in spite of considerable hydrocephalus she is a bright, intelligent girl. Her I.Q. is 101, and she has a good memory for past and recent events, except for a period of amnesia during her illness. She has a normal personality and excellent physique. Unfortunately she has bilateral optic atrophy and restricted visual fields, although her vision is good. Her pupils are dilated and fail to react to light.

CASE 7. This boy was found to be totally blind when he regained consciousness, and he remained blind for two months. His slight papilloedema did not appear to be the cause of the blindness. The second encephalogram taken during this time, however, showed considerable increase of the hydrocephalus which especially affected the posterior horns of the lateral ventricles (Figs. 16 and 16a). It was thought that the blindness was probably due either to the destruction or compression of the fibres of the optic radiation. His vision slowly returned and at present it appears to be normal. The child made a remarkable recovery and his mental development rapidly approached normal. Just before treatment was concluded a third encephalogram was performed. The appearances were strikingly better, the size of the ventricles being much less, similar to that shown on Fig. 14. The posterior horns of the lateral ventricles showed the greatest regression in size. This is the only case in which regression of the hydrocephalus was observed.

In addition to the hydrocephalus the spontaneous formation of a cyst was demonstrated within the substance of the frontal lobes in two cases (Nos. 3 and 4). The formation of a cyst in a parietal lobe was demonstrated in a 5-months-old infant two weeks after a ventricular puncture. This cyst was exactly at the site of the track of the needle (Figs. 17, 17a, and 18, 18a).

Correlation of Encephalographic Findings with Clinical Progress

After this survey of the cardinal findings it is interesting to compare the fate of the children in the two groups. For this purpose only those 44 patients will be considered who on September 30, 1950, have been observed for more than seven months from the beginning of treatment. Twenty-four (54%) of those 44 survived (Table 2).

TABLE 2
FOLLOW-UP PERIOD OF SURVIVORS ON 30.9.50*

Months	Number	
7– 9	4	7
9–12	3	
12–15	4	13
15–18	5	
18–24	4	
24–31	4	4
7–31	24	

* All survivors were alive on 20.1.51, a minimum of 11 months after the beginning of treatment.

Of the 18 children in whom the findings were consistently normal only two died, and only one of them from meningitis (Table 3). This boy was in a severely anergic phase and had practically normal

TABLE 3

CONDITION* OF CHILDREN WITH NORMAL AND ABNORMAL PNEUMOENCEPHALOGRAMS

Condition on September 30, 1950				Pneumoencephalogram	
				Normal	Abnormal
Alive	Recovered	Mentally normal	No neurological disability	13	—
			Optic atrophy	—	1
			Hemiplegia	—	1
		Retarded	No neurological disability	—	2
			Deafness	1	—
			Hemiplegia	—	2
			Hemiplegia and deafness	—	1
	Still under treatment			2	1
	Total alive			16	8
Dead				2	18
Total				18	26

* Minimum follow-up of seven months. All alive on 20.1.51.

cerebrospinal fluid throughout his illness except that a heavy growth of tubercle bacilli was obtained from almost all specimens of fluid examined. At necropsy there was but slight exudate and the ventricles were little larger than normal. This enlargement took place after the encephalogram was performed.

The second child was being treated for miliary tuberculosis at the time when meningitis developed. She responded well to treatment, and was discharged with a normal cerebrospinal fluid and radiographically and clinically normal lungs. Two months later she returned with fulminating phthisis and there was no response to further streptomycin treatment. At necropsy the meninges and the ventricular system were normal, but there were several small encapsulated subcortical tuberculomata.

Excluding two children still on treatment, 13 of the 16 survivors in the first group are physically and mentally normal. One acquired deafness during treatment before she could speak and consequently she is dumb as well. These handicaps obviously retarded her mental development, although there is reason to believe that she is retarded even beyond that.

Of the 26 patients with abnormal enecphalograms 18 (69%) died, all of them of meningitis. Excluding one child (Case 6) who is still on treatment, there are seven survivors in this second group. All of them have hydrocephalus. There is not one among them without some residual neurological or mental lesion. Only one child in this group has so far escaped death or major disability (Case 3). Three other children will probably be able to lead a useful, if restricted, life, in spite of their disabilities. The remaining three are so severely retarded that they are never likely to be able to fend for themselves.

This apparent close correlation between the encephalographic findings and the fate of the children must be assessed with regard to the severity of their disease at the beginning of the treatment. All cases were classified on admission into one of three groups, according to the criteria of the Medical Research Council (1948). This classification was used in the assessment of the results (Table 4).

Of the 44 children who have been followed for a minimum of seven months, 11 were classified as ' early,' 18 as ' intermediate,' and 15 as ' advanced ' cases. It is well established that most early cases will recover if adequately treated, but only a few in the advanced state will be saved. The prognosis is very doubtful in cases of intermediate severity.

In this series the initial encephalogram was within normal limits in all children in the early stage of the disease, but subsequently it became abnormal in one of them. This child and another died (of phthisis), but the remaining nine survived. Thus encephalography confirmed the good prognosis of this group.

Of the 15 advanced cases 13 had initially and permanently abnormal encephalograms. In only two was the first encephalogram normal and in one of these it became abnormal later. This last child and four others survived with the various disabilities which have been described, and ten died. Thus encephalography stressed the poor prognosis

TABLE 4

PROGNOSIS OF CHILDREN WITH TUBERCULOUS MENINGITIS CORRELATED WITH STAGE OF DISEASE AT BEGINNING OF TREATMENT AND ENCEPHALOGRAPHIC FINDINGS

Clinical Stage	Encephalograms Initial	Encephalograms Final	Number of Cases	Survivors	(%)
Early	Normal	Normal	10	9	(82)
	Normal	Abnormal	1	—	
	Abnormal	Abnormal	—	—	
Intermediate	Normal	Normal	7	7	(78)
	Normal	Abnormal	2	—	
	Abnormal	Abnormal	9	3	(33)
Advanced	Normal	Normal	1	—	
	Normal	Abnormal	1	1	
	Abnormal	Abnormal	13	4	(30)
Total	Normal	Normal	18	16	(77)
	Normal	Abnormal	4	1	
	Abnormal	Abnormal	22	7	(31)

of this group, both as regards chances of survival and the likelihood of residual defects.

The group between these two extremes is the most important because it is the largest and because of the uncertainty of the prognosis as judged by existing clinical criteria. At the best about half of them may recover but it is not possible to say which half. Of the 18 children in this group nine had initially normal encephalograms: seven recovered (78%) and the encephalograms became abnormal later in the two fatal cases. Of the nine with initially abnormal encephalograms only three are alive (33%) and one of them is an idiot. With the help of encephalography this group could be divided into two halves, one with a good and one with a bad prognosis (Table 4).

The last feature investigated was the prognosis of nine relapsed* cases of meningitis in relation to the pneumoencephalographic findings. The examinations were performed soon after the relapse. In five of them the appearances were normal and they survived. In the other four the appearances were abnormal. These are all dead.

Discussion

Certain objects of this investigation were set out at the beginning of this study and these will be examined in the light of the results presented.

(1) Over 100 reports on the treatment of tuberculous meningitis commented on the frequency of hydrocephalus. Many of them illustrated this by pneumoencephalograms or pathological specimens. Very few reports, however, mention that hydrocephalus is not an invariable finding. The reason for this is that pneumoencephalograms were usually performed in *selected* cases, either because some abnormality was expected or because the patient's clinical condition was unsatisfactory and surgical intervention was contemplated. This led to the belief that at least some degree of hydrocephalus is inevitable in all cases and this view was supported by Cairns (1949). Janbon, Bertrand, Salvaing, and Vernhet (1949), however, report that only 63% of their 55 patients had hydrocephalus, but no further details were given. Only two encephalographic studies reported the result in small series of unselected cases. Murano (1948) found normal ventricles in two out of 19 cases. Unfortunately the reproductions of his radiographs do not allow their critical assessment, but Schönenberg (1950) reproduced two encephalograms which appear to be normal and there were other similar cases in his series of 26.

It is because of this background, that the most

* 'Relapse' is used in a broad sense to denote the condition of children who were clinically well and whose cerberospinal fluid was either normal (two cases) or approaching normal (seven cases), but were not necessarily off intramuscular treatment at the time.

unexpected outcome of the planned investigation of this virtually unselected group of children was the frequency with which perfectly normal conditions were discovered. Yet there is no theoretical reason why ventricular dilatation should occur in the early stages of tuberculous meningitis before obstruction of the pathways has had time to develop. Nor does such an obstruction necessarily develop if treatment is promptly instituted. This was conclusively demonstrated in the early and some of the intermediate cases of meningitis of this series, where repeated examinations were performed. In approximately 40% of all cases no abnormal findings were present at any time.

The necropsy findings of streptomycin-treated cases of tuberculous meningitis are only of limited value as these cannot represent the conditions in the survivors. The findings in untreated cases are nearer to the conditions obtained in the living. Although most textbooks consider hydrocephalus as one of the characteristic features of the disease, some support for the observations of the present investigation may be found in the monograph on the pathology of hydrocephalus by Russell (1949a). She found only slight degrees of hydrocephalus in some cases of tuberculous meningitis, and in others there was none.

Lincoln (1947) was struck by the infrequency of hydrocephalus in cases where the duration of illness to death was less than three weeks (nine out of 40 cases, 22·5%). In cases of longer duration the incidence rose to 63·6% (14 out of 22). Perry (1950) reports a 31% incidence of hydrocephalus in his 80 cases. It is therefore reasonable to expect that these proportions need not be exceeded if effective treatment is given early in the disease.

(2) Obstructions were observed in more than half of the cases, either within the ventricular system, or, much more frequently, at the tentorial opening and in the subarachnoid cisterns. In this respect the present investigation fully confirms the encephalographic findings of Cairns (1949), Feld (1949), Janbon *et al.* (1949), and Smith *et al.* (1948). In pyogenic meningitis blockage of the Sylvian aqueduct or the foramina of Magendie and Luschka may occur, due to deposition of inspissated pus (Cairns, 1949), but obstruction at these sites was rarely found in this series, because of the clear nature of the fluid in tuberculous meningitis.

Great importance is attached to the absence of subarachnoid air as a sign of blockage at the tentorial opening. Feld (1949) also drew attention to this sign which he considered an indication for surgical intervention before hydrocephalus has time to develop. In the three cases of the present series where subarachnoid air was absent but with initially normal-sized ventricles, hydrocephalus developed in all. Whether any operative procedures would have been of value is unlikely in view of the published evidence (Feld, 1949).

(3) The incidence of hydrocephalus was almost the same as the incidence of obstructive lesions, and occurred in the same patients. This observation is in full accord with that of Russell (1949b) that an obstructive lesion can be found in at least 99% of cases of internal hydrocephalus. Nevertheless in four cases a moderate degree of hydrocephalus was observed in the presence of subarachnoid air and the absence of demonstrable obstruction, and such a case has also been illustrated by Feld (1949). This hydrocephalus is probably of the passive type and the ventricles merely enlarge to occupy the space left by the shrunken brain substance, due possibly to loss of nerve tissue as a direct result of coincident encephalitis or infarction. It is possible that this latter mechanism does play some part in the other much larger group of cases of hydrocephalus with a known obstructive element. Support for this suggestion may be found in the observation that appreciable enlargement of the head was rare even when the ventricles were of extreme size. There is no doubt, however, that obstruction is the dominant element in the production of hydrocephalus.

In only six cases of the present series did hydrocephalus develop in the course of treatment when normal encephalograms had been previously obtained, showing that early diagnosis may avert this frequent complication. Conversely, hydrocephalus, or the obstruction leading to it, was probably already present before treatment was begun in the large majority of the more advanced cases. This latter observation was more definitely established by Schönenberg (1950) who performed encephalograms on 26 patients before therapy. These facts strengthen the belief that intrathecal streptomycin plays no part in the causation of hydrocephalus, but merely renders it more obvious by prolonging the patient's survival (De, 1949).

One of the most important problems is the permanency of hydrocephalus in surviving patients. It is well established that even a considerable degree of hydrocephalus may regress if the obstruction giving rise to it is removed in time. Instances of this have been recorded by Fincher, Strewler, and Swanson (1948), Swanson and Perrett (1950), Torkildsen (1948), and Walker and Hopple (1949) in cases of cerebral tumour or stenosis of the Sylvian aqueduct, but regression of the hydrocephalus in tuberculous meningitis has not been previously described in the available literature. Of the six surviving cases of hydrocephalus repeated encephalograms showed no decrease in its degree

in two, and a substantial increase in three, in spite of considerable clinical improvement or indeed recovery of physical and mental health when the last encephalogram was performed. Cairns and Taylor (1949) had a similar experience with an adult patient. In one child in this series definite regression of the hydrocephalus was noted (Case 7), and consequently this may have occurred in others after the last encephalogram was performed. This problem is the subject of further investigations.

The aetiology of the spontaneous formation of a cyst in the brain substance in two cases is not quite certain. They may represent porencephalic cavities due to arteritis and infarction. Arteritis is a frequent pathological feature of tuberculous meningitis (Daniel, 1949; Doniach, 1949; Hektoen, 1896; Rigdon and Lefeber, 1950; Smith and Daniel, 1947; Winter, 1950), but there has been no description of arteritis leading to the formation of large cerebral cysts. Torkildsen's (1948) explanation is more likely. He reported on the spontaneous rupture of the ventricular ependyma in five cases of hydrocephalus due to cerebral tumour. This rupture was thought to have been caused by the difference between the high intraventricular and the low subarachnoid pressure and was followed by cyst formation. Cerebral cyst formations have been described in hydrocephalus of various aetiologies (Childe and McNaughton, 1942; de Lange, 1929; Penfield, 1929; Pennybacker and Russell, 1943; and Sweet, 1940) including one in an untreated case of tuberculous meningitis (Russell, 1949c). Torkildsen (1948) writes:

> Occasionally hydrocephalic patients give a history of sudden subsidence of the signs of increased intracranial tension which conceivably may be due to ventricular rupture with formation of a short circuit giving the cerebrospinal fluid direct access to the subarachnoid space.

It may be more than coincidence that the appearance of the cysts in the patients of the present series more or less coincided with a striking clinical improvement although actual communication with the subarachnoid space was not demonstrated.

Another case in this series supports the second theory. This infant had gross hydrocephalus, and at necropsy several ruptures were found in the ependyma of both lateral ventricles (Fig. 19), very similar to those of the case of Pennybacker and Russell (1943). It is assumed that there had been no time for cysts to develop.

(4) The correlation between the encephalographic findings, the stage of the disease, and the prognosis have already been analysed in detail (Tables 3 and 4). It is beyond the scope of this paper to correlate the encephalographic findings with all other factors which are generally thought to be of prognostic significance, e.g., age, coexisting miliary and other forms of tuberculosis, and the length of delay before treatment is instituted (Lorber, 1950c). In this series, however, encephalography was a very reliable single prognostic criterion. If taken together with all the other known factors, a correct prognosis may be given in almost all cases.

(5) Amatruda (1942) and Casamajor, Laidlaw, and Kozinn (1949) have pointed out that there is no definite correlation between encephalographic appearances and various degrees of mental development and that encephalography does not picture the functional capacity of the cerebrum. Amatruda noted that children with even gross communicating hydrocephalus may do particularly well from the standpoint of development. The observations of these authors apply to a large extent to the survivors of tuberculous meningitis in this series, but with certain reservations. Using the methods described elsewhere (Lorber, 1949) no apparent deterioration was detected in the intellectual capacity of 15 of the 16 survivors with normal encephalograms, but three of the eight survivors with variable degrees of hydrocephalus are severely retarded. It is interesting, however, that two children with considerable hydrocephalus have I.Q.s above 100. Although the numbers in this hydrocephalic group are small, it seems that mental deterioration is more frequent when ventricular dilatation is present.

(6) The most difficult problem is whether selection of cases for treatment and the abandonment of treatment on humanitarian grounds is justifiable or not. Many children live a vegetative existence for months, and streptomycin may not only unnecessarily prolong their suffering, but, worse still, may

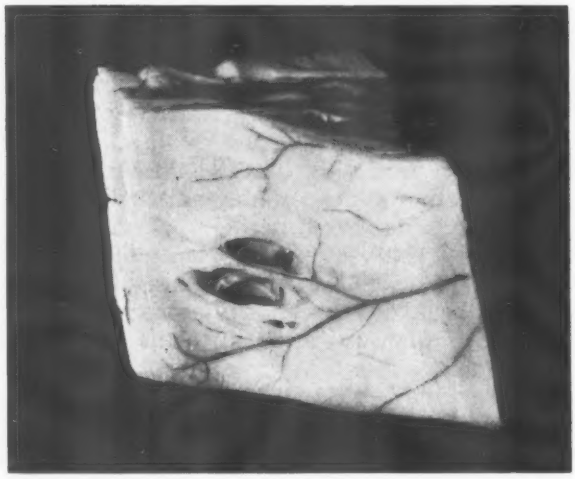


FIG. 19.—Spontaneous rupture of the ventricular ependyma in a case of tuberculous meningitis with gross hydrocephalus.

cure them of their infection and thus create serious social and moral problems. It would be of great practical advantage if one could recognize these cases early. Criteria are needed to define certain cases as untreatable, just as there are criteria for judging certain cancers inoperable. The observations in the present series suggest that encephalography may substantially contribute to the fulfilment of this need, but much more experience is necessary before any firm rules may be formulated. It is, however, probably advisable to interrupt treatment early where really gross hydrocephalus (Fig. 4) exists.

Summary

One hundred pneumoencephalograms were performed on 58 children suffering from tuberculous meningitis. With the possible exception of one case, no serious after-effects were noted. No relapse of the meningitis followed within two months of any examination.

In 18 children normal conditions existed four to 14 months after beginning the treatment.

Abnormalities were found in 36 children. In six of these a previous pneumoencephalogram had been normal. Three main abnormalities were detected.

(1) One or more blocks other than spinal ones were found in 30 cases. In all of these there was a block at the tentorial opening or in the basal cisterns. In two cases there was an additional block at the Sylvian aqueduct, and in three others in the foramina of the fourth ventricle. These blocks were usually present at or soon after the beginning of treatment.

(2) In no case of tentorial or basal cisternal block was there subarachnoid air. This sign preceded the hydrocephalus in three cases. In only four children was any degree of hydrocephalus seen when subarachnoid air was present. Subarachnoid air must be distinguished from subdural air which may occur in any encephalogram.

(3) Hydrocephalus of varying degrees was found in 34 cases. Clinical recovery was almost complete in eight of these children. Repeated pneumoencephalograms in six of them showed an increase in the degree of the hydrocephalus in three, no change in two, and a decrease in one.

In three hydrocephalic children cerebral cysts developed; in two cases spontaneously and in the other following a ventricular puncture. The aetiology of the cysts is discussed.

A close correlation was found between encephalographic appearances and prognosis. After a minimum follow-up period of eleven months 16 of 18 children with normal encephalograms were alive and only one of the survivors was left with serious neurological sequelae. One of the deaths was not due to meningitis.

Of 26 children with abnormal encephalograms only eight were alive after the same period of observation. They all have neurological or mental residual lesions, and these are serious in five.

Of nine cases of meningitis which relapsed, five had normal encephalograms and survived. The four others died.

No absolute dividing line was found regarding mental development following recovery from tuberculous meningitis in children with normal and abnormal encephalograms, but only one child out of 16 became retarded where the final encephalogram was normal, and three of eight children who survived with hydrocephalus are grossly retarded. In two cases considerable hydrocephalus was compatible with good intelligence.

It is suggested that further experience may well show that encephalography supplies criteria for the selection of cases for treatment and for the abandonment of treatment.

I wish to thank Professor R. S. Illingworth and Dr. T. Colver for permission to investigate their cases; Professor Illingworth, Dr. Honor V. Smith, Dr. S. A. Doxiadis, and Dr. D. G. H. Stone for their criticism; Dr. J. L. Emery for the pathological data; Dr. T. Lodge and Sister Mallinder for the radiographs; Mr. A. F. Taylor for the photographs and Mr. A. S. Foster for the line drawings.

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PYLORIC STENOSIS IN TWINS

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In 1938 Sheldon analysed 1,000 cases of hypertrophic pyloric stenosis and found 23 pairs of twins of which one or both had been affected. In this series one pair was monozygous and 12 dizygous. The type of twinning in the remaining pairs could not be decided. The evidence indicated that when pyloric stenosis affects monozygous twins both infants show the condition, but that when the twins are dizygous only one of the pair is likely to be affected. He recorded, in addition, one exception to this rule, namely, monozygous twins, only one of which was affected. The only previously recorded exception was by Lasch (1925). In this case no tumour was felt during life, and according to Sheldon the description of the post-mortem appearance of the pylorus left some doubt as to whether the condition was in fact hypertrophic stenosis.

In 1947 Laubscher and Smith reviewed 53 pairs of twins collected from the literature (including Sheldon's series) and found only one more exception, a dizygous pair both of which were affected. They found in all two exceptions in 13 monozygous pairs and one exception in 23 dizygous pairs. Since then two further exceptions to the rule have been reported. Garrison (1949) reported a pair of monozygous twins only one of which was affected, and Hughes, Small, and Macky (1949) reported a dizygous pair with both twins affected. There have been published six further examples of pyloric stenosis in twins which conform to the rule. Lamy, Pognan, Marillier, Jammet, and Cordier (1949) reported a monozygous pair in which both twins were affected. Dizygous pairs with one affected (three pairs) have been recorded by Cockayne and Penrose (1943), and one pair by Ward-McQuaid and Porritt (1950).

The purpose of this paper is to discuss the occurrence of the condition among monozygous and dizygous twins and to report four further pairs, all of which were exceptions to the rule mentioned above. In considering these cases it is obvious that two important questions must be answered: Is pyloric stenosis present in one or both of the pair? Are the twins monozygous or dizygous? In the majority of cases it is possible to give the answers with reasonable certainty. Sometimes, as the cases reported here will show, it may prove difficult. The problems presented by these questions will be briefly discussed before the cases are described.

The Diagnosis of Pyloric Stenosis

A positive diagnosis is usually easy, and the classical symptoms and signs are well-known. Moreover, since the treatment nowadays is nearly always surgical, an opportunity is given for confirming the presence of a pyloric tumour beyond all doubt.

It is more difficult to exclude the condition when the classical features are absent or present in a very mild degree. Wallgren (1937), Findlay (1937), Bexelius (1939), Malmberg (1939), and Lewis (1944) have published cases in which the anatomical deformity was present without symptoms, or in which the symptoms were mild and recovery spontaneous. One of the cases reported here was also symptom-free. Davison (1946) used the term 'manifest' pyloric stenosis to distinguish the typical cases from the symptom-free ones, and considered that the latter occur infrequently. There is, however, no evidence to show how often they do occur, for the condition might well escape notice unless it were specially looked for.

The observation of gastric peristalsis does not by itself justify the diagnosis, but palpation of a pyloric tumour is unequivocal. Radiology may be useful in doubtful cases (Miller and Ostrum, 1945; Olnick and Weens, 1949), although Wallgren (1946) has shown that in the preclinical stage radiological appearances may be normal in infants who later develop manifest pyloric stenosis.

It may not be possible or justifiable to subject an apparently healthy infant to repeated examinations, but it is suggested that the investigation should be as thorough as possible before the diagnosis of pyloric stenosis is excluded. This applies particularly when the condition appears in one of a pair of twins.

Determination of Type of Twinning

The problem of stating with any degree of certainty whether twins are monozygous or dizygous may also present some difficulty. Ford, Brown, and McCreary (1941) pointed out that the determination of the type of twinning in published cases is often inadequate. The conclusion is based on the sex, birth membranes, physical resemblance and blood groups, but in many reports the evidence is scanty and few details are given. The description of the placenta may be misleading, as information is often incomplete and a detailed examination is usually not made at the time of birth. It is possible for monozygous twins to have separate placentas and for dizygous twins to have their placentas fused so as to appear single. A comparison of physical characters is difficult in infancy, particularly when the progress of one twin has been interrupted by illness.

Case Histories

Family 1. Monozygous twins, one affected. Born July 12, 1948. Second pregnancy (one stillbirth previously). No family history of pyloric stenosis. Parents not consanguineous.

TWIN A. Boy. Birth weight 5 lb. 6 oz. Bottle fed since 2 weeks old. Sudden onset of projectile vomiting when 37 days old, followed by constipation and loss of weight. Admitted nine days later. Gastric peristalsis was seen, a pyloric tumour was felt, and at operation a typical pyloric tumour was discovered.

TWIN B. Boy. Birth weight 5 lb. 5 oz. Bottle fed since 2 weeks of age. Thrived and gained weight normally. There was an occasional regurgitation of feeds during the sixth week, but never any vomiting. Admitted to hospital with his twin, and during the eight days under observation no abnormality was detected. He was examined for the presence of peristalsis or a tumour, but neither was found.

The twins were seen again at 3 months of age and at 1 year and both were progressing normally. Twin B had remained free from symptoms.

Family 2. Monozygous twins, one affected. Born April 20, 1949. Fourth pregnancy (one boy, 9 years old, and one girl, 6 years, both well: abortion 18 months previously). No family history of pyloric stenosis. Parents not consanguineous.

TWIN A. Boy. Birth weight 7 lb. Bottle fed. Projectile vomiting associated with constipation began when 21 days old. Admitted to hospital two weeks later. Gastric peristalsis was seen and a pyloric tumour felt. At operation a small pyloric tumour was found. For three days the infant did well, but post-operative complications occurred and he died three weeks later. At necropsy the presence of a pyloric tumour was confirmed.

TWIN B. Boy. Birth weight 7 lb. Bottle fed. Thrived and gained weight normally, with no vomiting or constipation. He was examined during feeds on two occasions (aged 41 and 58 days) and no peristalsis or tumour was detected. On the second occasion a barium meal was given but no abnormality could be seen. At two hours the bulk of the meal was in the small intestine, and at three hours only a few flecks were left in the stomach. At 10 weeks old his own doctor reported that he was still free from symptoms.

Family 3. Dizygous twins, both affected (one symptom-free). Born May 13, 1949. Third pregancy (one boy, died at birth with 'deformed head,' one girl, 18 months old, well). No family history of pyloric stenosis. Parents not consanguineous.

TWIN A. Boy. Birth weight 6 lb. 8 oz. Bottle fed. Sudden onset of projectile vomiting when 19 days old. On admission five days later gastric peristalsis was seen and a pyloric tumour felt. At operation a small hard tumour was found. Recovery was uneventful.

TWIN B. Boy. Birth weight 6 lb. 8 oz. Bottle fed. He thrived and gained weight normally with no vomiting or constipation. First examined aged 32 days when peristalsis was clearly seen during a feed, but no tumour could be felt. A barium meal was given the same day and vigorous gastric peristalsis was seen, but no other abnormality detected. The stomach was empty of barium in two and a half hours. The infant was examined again when 51 days old, and on this occasion a small pyloric tumour was felt by several experienced observers. He was last seen at 6 months old and had remained free from symptoms.

Family 4. Monozygous twins, one affected. Born June 13, 1949. Third pregnancy (one girl, 4 years old, well; one stillbirth). No family history of pyloric stenosis. Parents not consanguineous.

TWIN A. Girl. Birth weight 4 lb. 6 oz. Breast fed until onset of vomiting at 17 days. At 21 days she was admitted to hospital, a small, feeble and wasted infant weighing 3 lb. 6 oz. Peristalsis was seen and a pyloric tumour felt. At operation a typical pyloric tumour was found.

TWIN B. Girl. Birth weight 4 lb. 6 oz. Breast fed. Thrived and gained weight normally. There was an occasional small vomit during the second week of life, but no other symptoms. At 2 months of age she was examined during a feed, but no abnormality was discovered. No further investigations were carried out, but she was seen again at 6 months and was still free from symptoms.

Discussion

It is generally agreed that genetic factors play some part in the pathogenesis of pyloric stenosis, but their exact role is not understood. The problem has been discussed by Cockayne and Penrose (1943) who suggested that the incidence is determined by a recessive gene whose manifestation is influenced by birth order and sex. It is further considered by Carter and Savage elsewhere in this issue. A study of the occurrence of the condition in twins may contribute something towards the eventual solution of this problem.

Incidence of Pyloric Stenosis in Twins. Sheldon (1938) found 23 pairs among 1,000 cases of pyloric

stenosis. One twin only was affected in each of 22 pairs, and in the remaining pair (the only one known to be monozygous) both were affected. There were therefore 24 affected twins among 1,000 cases, a ratio of 1 to 40·7. The incidence has been recorded in three other series. Ford *et al.* (1941) found 14 affected twins in 12 pairs among 436 cases, Monrad (1927) found three affected twins in three pairs among 228 cases, and Cockayne and Penrose (1943) found 13 affected twins in 11 pairs among 449 cases. If the four series are combined we get a total of 54 affected twins in 49 pairs among 2,113 cases of pyloric stenosis, a ratio of 1 twin to 38·1 babies born singly.

Laubscher and Smith (1947) pointed out that if there is one twin birth for every 80 single births, there are two twin babies for every 82 babies born, i.e. 1 in 41, or a ratio of 1 to 40. This is practically the same as the ratio of twins to babies born singly among the affected babies. In other words, the incidence of pyloric stenosis is the same in twins as in infants born singly. It is not twice as great as had been suggested by previous writers.

Occurrence in Monozygous Twins. Adding our cases to those previously reported (excluding those of Lasch as uncertain), we find that out of 17 monozygous pairs there are five in which only one twin was affected. The difficulty of determining the type of twinning with certainty has been stressed in this paper, but the evidence in these five pairs is in favour of monozygosity. Sheldon's pair had one placenta without any line of fusion and one set of membranes; the appearance of the twins was exactly the same; the finger-prints were not identical, but this has little significance. His account leaves little doubt that the twins were monozygous. Garrison's pair of negro twin girls had a single chorion and two amnions. A comparison of physical measurements at 20 months showed slight differences only, and a photograph of the twins at that age demonstrates great similarity of appearance. Detailed evidence of the type of twinning of the three pairs reported in this paper is given in the appendix.

There is no doubt that the diagnosis of pyloric stenosis was correct in the affected twins of the five pairs, for each case was confirmed at operation. The possibility must, however, be considered that the unaffected twin of each pair had hypertrophy of the pylorus without symptoms. Sheldon mentioned this, but in the absence of either symptoms or signs considered it unlikely in his case. Garrison considered that his unaffected twin might have fallen into this category. There were no symptoms, but he makes no mention of clinical examination or other investigation. In our three pairs the unaffected twins were examined with this possibility in mind, but no evidence of pyloric hypertrophy could be demonstrated. (In family 4 the unaffected twin was not seen until 2 months old, but one would expect a tumour, if present, to persist until this age.) It is interesting that Lewis's (1944) asymptomatic case was one of monozygous twins, the other one having manifest pyloric stenosis.

To sum up, there are at least five published pairs of twins, which can be accepted as monozygous, in which only one twin was affected. It therefore seems that the rule that both are usually affected does not hold good. It is not suggested that five out of 17 represents the true proportion of discordant monozygous pairs, for these are more likely to arouse interest and be reported.

Whatever part genetic factors play in the pathogenesis of pyloric stenosis, monozygous twins must be equally affected. To find a considerable number of monozygous pairs with only one twin affected is therefore surprising. It can be explained in one of two ways. The unaffected twin may in fact have hypertrophy of the pylorus but remain symptom-free. In this case the conditions (presumably post-natal) necessary for the development of symptoms must be present in one twin and not the other. It is known that asymptomatic cases do occur, but we were unable to discover any evidence of pyloric hypertrophy in any of our unaffected twins. This leads us to favour the alternative explanation, which is that one twin remains normal while the other is affected. If this is so, the development of pyloric stenosis must depend in part on the presence of an environmental factor which can act on one twin and not the other. This could be either prenatal or post-natal.

Occurrence in Dizygous Twins. Adding our case to those previously published, we find both twins affected in three out of 29 dizygous pairs. From a genetic point of view dizygous twins stand in the same relation to each other as ordinary siblings. Cockayne and Penrose (1943) found a definite familial incidence, which they put at 1 in 20. We might expect therefore to find that a small proportion of dizygous twins is concordant. Three out of 29 is probably rather a high proportion, but concordant pairs are more likely to be reported.

The number of pairs of twins published so far is comparatively small, and before any final statement can be made about them many more will have to be studied.

Summary

Four pairs of twins affected by pyloric stenosis are reported. Three were monozygous with one of each pair affected. One was dizygous with both twins affected.

Including these cases, there have been published in the literature 17 monozygous pairs of which five had only one twin affected, and 29 dizygous pairs of which three had both affected. Figures are quoted which show that the incidence of pyloric stenosis is the same in twins as in infants born singly.

Some points concerning the diagnosis of pyloric stenosis and the determination of the type of twinning are considered. The latter is further discussed in an appendix.

APPENDIX

There is no difficulty in classing twins as dizygous when they are of opposite sex, but the correct classification of twins of the same sex may not be easy.

The state of the membranes does not help much since about a third of monozygous twins are dichorial (von Verschuer, 1939). Probably the only definite conclusion that can be drawn from the state of the membranes is that in those cases where there is anastomosis between the circulations in the placenta, or only a single chorion can be demonstrated microscopically, the twins are monozygous.

Physical examination of the twins is usually more helpful, but it is easier to come to definite conclusions from such an examination in older children than in infants. Though monozygous twins will

TABLE 1

DISTRIBUTION OF CHARACTERS IN THE FOUR FAMILIES

		Family 1	Family 2	Family 3	Family 4
Blood Group	Twin 1	A1 CDecde. MsMs. Kell−. pp.	A. D. MN.	O. cdecde. MSNs. Kell−. pp. Lu−.	O. CDecde. NsNs. Kell−.pp. Lu (a+).
	Twin 2	A1 CDecde. MsMs. Kell−. pp.	A.D. MN.	O. CDecde. MsNs. Kell−. pp. Lu−.	O. CDecde. NsNs. Kell−. pp. Lu (a+).
	Father	A1 cdecde. MsMs. Kell−. Pp.	O. D. MN.	O. cdecde. NsNs. Kell−. Pp. Lu−.	A1. cDEcde. NsNs. Kell−. pp. Lu (a+).
	Mother	A1 CDeCDe. MsNs. Kell−. pp.	A.D. MN.	O. CDecde. MSMs. Kell−. pp. Lu−.	O. CDeCDe. MsNs. Kell—.Pp. Lu. (a−).
Hair	Twin 1	Light red-brown	Light brown	Fair, curly	Light red, wavy
	Twin 2	Light red-brown	Light brown	Fair, curly	Light red, wavy
	Father	Dark brown (reddish as a boy)	Black (since infancy)	Dark red-brown, curly	Dark brown, wavy
	Mother	Light brown (no red)	Brown	Medium brown, curly	Light red, straight
Eyes	Twin 1	Blue	Dark blue	Blue-grey	Blue-grey
	Twin 2	Blue	Dark blue	Blue-grey	Blue-grey
	Father	Hazel	Brown	Brown	Hazel
	Mother	Green	Brown	Blue-grey	Red-brown
Nail Shape	Twin 1	Broad	Long	Broad, square	Long
	Twin 2	Broad	Long	Broad, triangular	Long
	Father	Broad	Long	Medium	Long
	Mother	Long	Long	Broad, square	Broad
Ear Lobe	Twin 1	Free	Attached	Free	Free
	Twin 2	Free	Attached	Free	Free
	Father	Attached	Attached	Attached	Free
	Mother	Attached	Free	Attached	Attached
Frontal Suture	Twin 1	Keeled	No ridge	No ridge	No ridge
	Twin 2	Keeled	No ridge	No ridge	No ridge
	Father	No ridge	No ridge	No ridge	No ridge
	Mother	Keeled	No ridge	No ridge	No ridge

ultimately have very similar skeletal measurements, this is not true at birth and in early infancy; where one twin is ill and malnourished such differences may be accentuated. Again differences in maturation make such criteria as hair colour and eye colour, characters which may change rapidly in infancy, less reliable than in adults. Finger prints and iris pattern are difficult to record and read in infancy.

The most valuable single characters are undoubtedly the blood groups. If the twins differ in any group they are dizygous. If they are the same for all groups, and the genotype of the parents' blood groups is known, it is possible to give a figure for the probability that they are monozygous. The other characters listed in Table 1 are genetically determined, but the exact mechanism of inheritance is not known. For each of these characters in which the parents differ, resemblance of the twins increases the likelihood that they are monozygous, but no exact figures can be calculated for the probabilities involved.

Family 1. These twins were seen at 16 months of age. They resembled each other very closely indeed in body build, teeth pattern, and iris pattern as well as in the listed characters. While the blood groups do not provide strong evidence here (the odds are 3 to 1 on monozygosity) there is little doubt that they are monozygous. There was said to be one placenta.

Family 2. These twins were seen at 3 weeks of age. The death of one twin prevented any follow-up and complete investigation. The state of twinning must remain in doubt but it is more likely that they were monozygous than dizygous. From the MN blood groups the odds are 5 to 3 on monozygosity, and the hair colour adds some support. The doctor who delivered the twins reported that there was one placenta.

Family 3. These twins were seen at 5 weeks and again at 8 months of age. The blood groups make it certain that they are dizygous. When first seen the only obvious difference was in the nail-shape, but at 8 months the noses and mouths differed in size and shape, though the ears were still very much alike. The doctor who delivered them reported that there was one placenta with a line down the middle which he did not think indicated real cleavage.

Family 4. These twins were seen at 4 weeks and at 7 months of age. They are very probably monozygous. The odds from the blood groups are 31 to 1 on monozygosity, and there is supporting evidence from each of the characters listed. Twin 2, the affected twin, was still 1 lb. lighter and ½ in. shorter and had slightly fairer hair when seen for the second time. The doctor who delivered the twins reported that there was one placenta.

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PYLORIC STENOSIS IN FOUR FIRST COUSINS

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Although the cause of congenital pyloric stenosis is not known, there is good evidence that one or more genetic factors play a part. This evidence may thus be summarized.

Incidence in Twins. Large series of twin pairs are not yet available for analysis, since it has only recently been realized that the state of the foetal membranes is not a reliable guide to the type of twinning. The reported cases and four additional pairs are discussed by Powell in another paper (page 45). However, it appears that pairs of monozygous twins are more often both affected with pyloric stenosis than are pairs of dizygous twins of like sex, so genetic factors play some part. It is also clear that monozygous twin pairs are not always both affected. Therefore if genes are responsible they do not always manifest themselves.

Incidence in Siblings. Brothers and sisters, other than twins, of children with pyloric stenosis are themselves not uncommonly affected. The general incidence in England of pyloric stenosis is probably about 1 in 400 live births. A survey in Newcastle gave the figure of 2·8 per 1,000 live births (Davison, 1946), yet in a survey in which the homes of 212 affected children were visited it was found that at least seven of 324 non-twin siblings had also had the disease (Cockayne and Penrose, 1943).

The incidence in brothers and sisters of affected children is higher than that in the general population. But it is also clear that if a single gene is concerned the rate of manifestation is low.

Incidence in Other Relatives. Occasional reports of affected pairs of relatives other than siblings have appeared; for example, parent and child (Ashton, 1929) and pairs of first cousins (Cockayne, 1934). But it is not clear that these are more than chance occurrences. If 200 affected children had 1,000 first cousins one would expect to find a few of these affected even if the true incidence among them was

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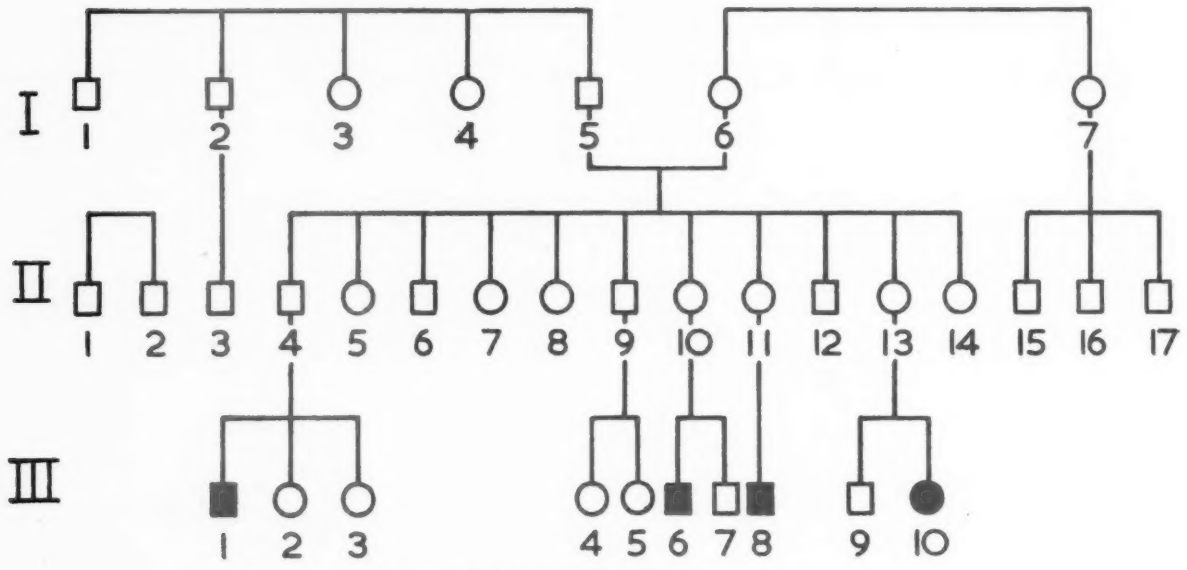

FIG. 1.—Pedigree of the affected family.

only that of the general population. No surveys have been made which enable us to compare the incidence in parents and first cousins of affected children with the general incidence. At a time when pyloric stenosis was usually lethal one would not expect to find many instances of affected individuals having children. In a series of 480 children treated at The Hospital for Sick Children, Great Ormond Street, London, between 1943 and 1947, it was recorded on two occasions that the father also had the disease. But before very long we should know how often the children of individuals with pyloric stenosis are themselves affected.

Clinical Material

We have encountered a remarkable family where five of a family of 11 brothers and sisters have had children and four of them have had a child with pyloric stenosis. The condition in each child was diagnosed and confirmed at operation in The Hospital for Sick Children.

The essentials of the family tree are shown in Fig. 1.

In collecting this family tree visits were paid to the homes of the grandparents I 5 and I 6, also of the parents II 4, 10, 11, 13, and their spouses. None of the spouses had been affected themselves and none of their near relatives had had an illness suggestive of pyloric stenosis. There were no consanguineous marriages in either parental or grandparental generation.

Discussion

This family was discovered in the course of a search for examples of twinning and pyloric stenosis. Four hundred and eighty case records were examined. The mother of the fourth child told the physician at the initial interview that she thought that three of her nephews and nieces had been affected.

If the cause of pyloric stenosis were purely environmental it would be an extraordinary coincidence that these four children should be affected. If inherited factors play a part it is a less improbable event, but still remarkable on any simple genetic hypothesis. If a dominant gene were responsible it is surprising that no member of the two preceding generations was affected, whereas if a recessive gene were responsible each of the four brothers and sisters must have married a carrier. At first sight this seems most unlikely, but if the incidence of pyloric stenosis is 1 in 400 and the incidence in siblings of affected children is about 1 in 30 then a high proportion of the population (about 1 in 7) must be carriers on the recessive gene hypothesis.

Summary

There is evidence that genetic factors play some part in the causation of pyloric stenosis. Identical twins appear to be more often both affected than fraternal twins of like sex, and the incidence in brothers and sisters of children with pyloric stenosis is higher than in the general population.

A family of 11 brothers and sisters is presented, five of whom have had children, and of these four have had a child with pyloric stenosis in which the diagnosis was confirmed at operation.

This family provides additional evidence that genetic factors are in part responsible for the condition. Also it suggests that if a recessive gene of incomplete manifestation is at work then a high proportion of the population must be carriers.

We wish to thank the visiting staff of the hospital for permission to make use of the records of their cases, and also the clerical staff of the follow-up department for their patience in collecting the large numbers of records involved.

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TWO CASES OF ADRENAL HYPERPLASIA WITH ADRENAL CORTICAL INSUFFICIENCY

BY

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The adreno-genital syndrome in infancy is associated almost invariably with bilateral adrenal hyperplasia. The characteristic syndrome is a combination of hyperfunction of the genital hormones of the suprarenal, producing precocious virilism in males and pseudohermaphroditism in females, and hypofunction of the salt-water hormones resulting in an electrolyte imbalance of the Addisonian type. Glucose metabolism is usually unaffected. The condition has been frequently reported in two or more siblings. A general review of the subject has been written by Wilkins (1948).

There are numerous cases described in the literature of adrenal hyperplasia in older children or adults with sexual changes, but no symptoms of adreno-cortical insufficiency. We do not propose to discuss these further, although it would be of interest to know details of the progress in infancy of such cases.

Symptoms due to Adreno-cortical Insufficiency. The classical picture is of normal progress in the first week of life. The first symptom is usually vomiting, which may start at any time between one and six weeks, and is occasionally projectile in character. Several cases are recorded of laparotomy being performed for suspected pyloric stenosis or intestinal obstruction, and our second case was treated with pylostropin at one period. Associated with the vomiting there are usually small loose stools often containing mucus, marked lethargy, pyrexia, and frequently sweating. Dehydration appears early and is disproportionately great for the degree of vomiting. The symptoms are usually insidious in onset but become suddenly and dramatically worse, usually terminating in death between six and 12 weeks in untreated cases. The clinical picture is closely similar to that of Addison's disease, except that the glucose metabolism is usually normal (Wilkins, Fleischmann, and Howard, 1940; Jacobsen, Koepf, Talbot, and Wilkins, 1949). Pigmentation of the skin sometimes occurs (Butler, Ross, and Talbot, 1939; Wilkins *et al.*, 1940). The clinical syndrome was first brought to general notice by Dijkhuizen and Behr in 1940, and since then fairly numerous reports have been made.

Biochemical Findings. Evidence that the symptoms were associated with low serum sodium and chloride levels and high serum potassium levels was provided by Butler *et al.* (1939) in a case later confirmed by laparotomy, and by Thelander and Cholffin (1941 and 1946) in a child who was kept alive till 6 years of age and died in an attack of measles. Two of the four cases recorded by Zuelzer and Blum (1949) had also had biochemical investigations. Cases with similar clinical and biochemical findings, where hyperplasia of the adrenals was probable but not proved, have also been reported (Darrow, 1943-4; Jacobsen *et al.*, 1949). The largest group of cases are those not diagnosed during life and without biochemical investigation, but where the clinical history leaves little doubt that the symptoms were due to adreno-cortical insufficiency (Allibone, Baar, and Cant, 1947; Skelton, 1945; Blackman, 1946).

Cases with Adreno-cortical Insufficiency. The sexual changes are precocious development in boys and pseudohermaphroditism in girls. We give later the reasons for thinking that these changes are probably due to hyperplasia of the reticular zone. Only one definite case has been reported in a female with normal external genitalia (Dijkhuizen and Behr, 1940). Males usually appear normal at birth, but penile enlargement and sometimes pubic hair develop within a few weeks (Thelander and Cholffin, 1941 and 1946; Butler *et al.*, 1939). Few investigations of the ketosteroid output have been recorded in these cases. Talbot, Albright, Saltzman, Zygmuntowitz, and Wixom (1947) in a male of 8 years found a urinary 17-ketosteroid output of about 200 mg., and an 11-oxycorticosterone level of 0·36. Darrow (1943-4) in a male of 6 months found a urinary 17-ketosteroid output of 2·5 mg. Zuelzer and Blum (1949) comment that it would be worth investigating the urinary hormones of the mother in these cases. Jacobsen *et al.* (1949) says

that the maternal hormone output is normal but gives no references. Premature ossification of the carpal bones may occur (Wilkins *et al.*, 1940 ; Darrow, 1943-4), but is not invariable and was absent in our first case and in two cases of Allibone *et al.* (1947). No radiographs were taken of our second case.

Histology of the Normal Adrenal

In the newborn child the adrenal cortex consists of three distinct zones: zona glomerulosa, zona fasciculata, and foetal reticular cortex. The last layer is the thickest and is composed of large lipoid-free cells resembling normal liver cells. Involution of this zone begins soon after birth and is often complete within two months of birth (Parkes, 1945) and certainly by the age of 1 year (Lewis and Pappenheimer, 1916). It is gradually replaced by the adult reticular cortex which is largely made up of granular eosinophilic cells containing lipoid but also including many cells with more deeply eosinophilic cytoplasm and hyperchromatic nuclei. Both types may contain brownish pigment.

Apart from the different arrangement of the cells in the various layers, it is possible to differentiate adult and foetal reticular tissue from each other and from the other zones by the characters of their individual cells. Even so, in the presence of hyperplasia of the cortex, there is frequently considerable difference of opinion as to which zone shows the greatest increase.

Grollman (1936) divides the cells of the cortex as a whole into two types: the interrenal cells, deficiency of which causes Addison's disease, and cells producing androgens. The differentiation of these cells is not satisfactory although Broster and Vines (1933) have claimed to distinguish androgenic cells by staining granules in their cytoplasm by the Ponceau-fuchsin technique. The specificity of this has been upheld by several observers (Allibone *et al.*, 1947; Zuelzer and Blum, 1949), whereas others consider that it merely reflects the degree of eosinophilia and the lack of lipoids in the cytoplasm (Wilkins *et al.*, 1940; Sudds, 1940; Flynn, 1942).

Functions of the Zones of the Cortex. Attempts have been made to identify the various zones with the production of specific hormones. Experiments on rats suggest that the zona glomerulosa produces a hormone influencing electrolyte and water regulation and probably closely allied to 11-desoxycorticosterone (Swann, 1940; Greep and Deane, 1947; Deane, Shaw, and Greep, 1948). These workers found that rats on a low sodium or a high potassium intake developed hypertrophy of the zona glomerulosa and shrinkage and disappearance of the ketosteroid droplets. They also found that the zona glomerulosa underwent shrinkage and atrophy if DOCA injections (2 mg. daily) were given for a month. There is some evidence that the zona fasciculata is the source of a hormone responsible for controlling carbohydrate, fat, and protein metabolism (Jacobsen *et al.*, 1949).

It is now generally agreed that the reticular zone is the origin of the masculinizing hormones. This is borne out by the fact that virilism and hyperplasia of the reticular zone are frequently associated (Broster, Hill, and Greenfield, 1932; Goldzieher and Koster, 1935; Young, 1937; and others) and by the experimental work of Howard (1937). These hormones have an action similar to that of testosterone and are the probable precursors of the urinary 17-ketosteroids. They are not normally produced until about the eighth year of life.

Gross Appearance and Histology of Adrenal Glands in Adrenal Hyperplasia

In the adreno-genital syndrome the adrenal glands show gross enlargement due to thickening and duplication of the cortex. In the majority of cases the combined weight of the adrenals is 10-20 g. although weights up to 34 g. have been reported (Dijkhuizen and Behr, 1940). Aberrant hyperplastic cortical tissue has been frequently noted.

Histology. The interpretation of the histology of the hyperplastic cortex has led to several different conclusions. Wilkins *et al.* (1940) considered that the cortex in their case was distorted by the replacement of the normal zones by masses of androgenic cells of the prenatal reticular type. Blackman (1946) believed that there was hyperplasia of reticular cortex of adult type, and Allibone *et al.* (1947) found variations between different cases, some having a well-marked reticular zone of adult type and others a hyperplastic transient cortex. These findings suggest that both the foetal and adult types of zona reticularis produce androgens. A reticular cortex composed of cells of varying size and shape, including many bizarre giant cells, was observed by Dijkhuizen and Behr (1940). Although the majority of observers are agreed that the hyperplasia is on the part of the reticular cortex, either of adult or prenatal type, others have come to the conclusion that the zona fasciculata was thickened in the presence of a zona reticularis of normal size (Skelton, 1945; Zuelzer and Blum, 1949). The genital abnormalities indicate that excessive androgens are active as early as the eleventh to the twelfth week of foetal life. The anatomical development of pseudo-hermaphroditism due to excess androgens is well illustrated in the article of Jacobsen and his colleagues (1949). In view of the possible production of

the electrolyte and water controlling hormone by the zona glomerulosa the histology of this zone in cases of hyperplasia with Addisonian crises assumes a greater interest. Occasional cases have been described in which the glomerular zone was thin or absent (Dijkhuizen and Behr, 1940; Skelton, 1945; Blackman, 1946) and this deficiency has been held to be the cause of the Addisonian crises. This view has been particularly upheld by Zuelzer and Blum (1949), who found the glomerular zone to be completely absent in four infants. However, a similar finding has been reported in adults with adrenal hyperplasia but without Addisonian symptoms (Blackman, 1946). Jacobsen *et al.* (1949) have pointed out that excessive production of a particular cortical steroid may partially cancel the physiological effects of others. The production of the hormone regulating salt and water metabolism may be normal but its effect may be inhibited by the presence of excess androgens, in which case a histological change in cells producing hormones other than androgens would be unlikely. On the other hand, it is conceivable that the adrenal may secrete a hormone causing excessive excretion of salt rather than its retention, as was suggested by the work of Lewis and Wilkins (quoted by Jacobsen *et al.*, 1949). Changes in other endocrine glands are not striking. Involution of the thymus has been noted in many cases. It is, however, a common finding in infants dying after prolonged illness and is probably of little significance. The anterior pituitary may show a relative preponderance of basophil cells, but, in the absence of accurate cell counts, the significance of this finding cannot be assessed.

Case Reports

Our two cases were both female pseudohermaphrodites with Addisonian crises, but despite this they pursued very different clinical courses. Because we feel that the possible variations in the clinical course have not been sufficiently emphasized before, and think that there is a probable correlation between the clinical and histological patterns in the two cases, we are describing them in detail. The first case was diagnosed on the first day of life and energetic replacement therapy with salt and cortical extract was attempted after the first crisis, but control was never satisfactory and the infant died at 57 days. The second case was not diagnosed during life, and despite having only erratic amounts of saline at irregular intervals and no cortical extract, survived to 261 days. (The clinical diagnosis of this case was rendered much more difficult by the more insidious nature of the symptoms, the much less definite evidence of pseudohermaphroditism, and also by lack of facilities for biochemical investigation in the hospital in which she was treated.)

The two infants appear to represent two of many possible gradations between those cases of adrenal hyperplasia with electrolyte imbalance sufficiently fulminating to cause death in the first two weeks of life, and those where no evidence of electrolyte imbalance can be found.

Case 1 (R.H.). The infant was born at the Mothers' Hospital, London, on February 9, 1949. Birth weight was 7 lb. 3 oz. (3,260 g.). Both parents were healthy and there was one normal female sibling aged 6 years. Family history, pregnancy, and labour were normal. In general appearance (Fig. 1) the infant was thin and worried-looking from birth and had a fairly profuse growth of scalp hair. The skin never showed any pigmentation. The abnormal external genitalia (Fig. 2), which conform to the type frequently described, were noted at birth, and the infant was diagnosed as a female pseudohermaphrodite by Dr. Helen Mackay, who suggested that this might be a case of adrenal hyperplasia. The urethral orifice was in the position of perineal hypospadias and was very small, only admitting a No. 2 ureteric catheter. There was a blind dimple at the tip of the enlarged clitoris.

The pulse was regular and of good volume; the heart was not enlarged, and sounds were normal. The blood pressure was not taken before symptoms developed. All other systems appeared normal.

PROGRESS. The infant seemed normally vigorous during the first week of life, and sucked well. The serum electrolyte levels at 6 days were normal (Serum Na, K, Cl and HCO_3). At 7 days she developed pyrexia, loose stools, and some vomiting, and was treated by a 24-hour withdrawal of milk feeds. Vomiting, which was never projectile, persisted two to four times a day throughout life. For the next ten days there was slowly increasing lethargy, sweating, and slight pyrexia. These symptoms were not recognized as being due to adreno-cortical insufficiency, partly because of the normal biochemical findings at 6 days, and partly because pyuria was present. The pus cells probably came from the vagina, but a urinary infection was diagnosed and penicillin and sulphatriad given. A catheter specimen two days later was clear.

At 18 days the infant, who had been slowly deteriorating, became suddenly collapsed and dehydrated, and vomiting increased. The pupils were markedly contracted. A most dramatic improvement occurred following saline and eucortone therapy. Next day the infant seemed almost normal apart from some oedema and a soft systolic murmur which was heard irregularly thenceforward. Saline intake was reduced, and stopped at 27 days in an effort finally to establish that the symptoms were due to an electrolyte imbalance of the Addisonian type. Again there was slowly increasing lethargy, sweating, and dehydration.

The second crisis at 30 days was associated with low serum sodium and chloride levels, while the urinary

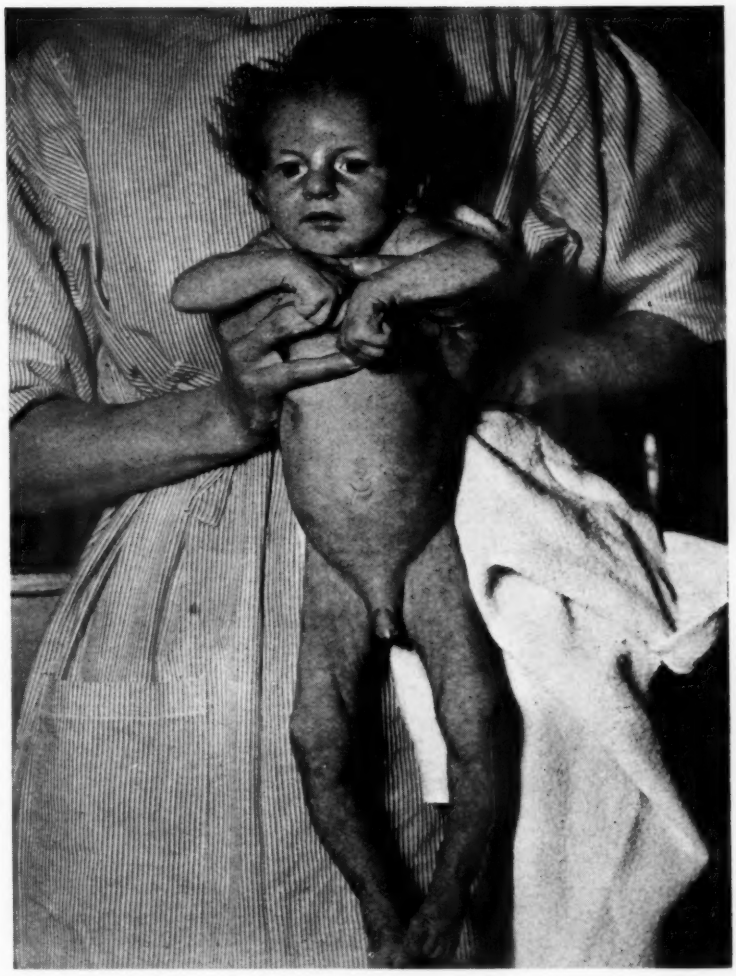

FIG. 1.—Case 1, aged 42 days. Photograph showing general appearance; thin infant; worried expression; fairly profuse hair; slightly distended abdomen.

chlorides were 4 g. per litre. Temporary improvement occurred with the administration of oral saline, but was not maintained.

The third crisis occurred at 41 days and eucortone was given again. At 42 days cardiac irregularity was noted for the first time, starting with inconstant 1:4 dropped beats, and progressing to gross coupled rhythm at 44 days. This crisis responded poorly to therapy, and at 43 days severe acidosis developed while the serum potassium remained high (CO_2 13·1 m.eq./litre; Cl 131·6 m.eq./litre; K 9·101 m.eq./litre; Na not done). Eucortone was stopped and saline intake reduced, and by 44 days the serum electrolyte levels were normal. Marked coupled rhythm persisted, shown by electrocardiography at 45 days to be due to alternate auricular extra-systoles (Fig. 3). Inconstant abdominal distension, sometimes gross, was noted from 41 days until death. Oral feeding was begun again. Saline intake was maintained at approximately 2 g. per day. (The amount of NaCl given in the milk has been ignored throughout.) Percortin was substituted for eucortone and was given in a dose of 0·2 ml. per day. Slight improvement occurred and the cardiac rhythm became normal. At 50 days cardiac extra-systoles recurred, and there was some acidosis, and at 53 days the fourth crisis developed following a rise of serum potassium to 10·79 m.eq. (42 mg.) at 52 days. The blood pressure on this day was 90/60 mm. mercury (right leg). Therapy was changed to eucortone 5 ml. four-hourly and intravenous saline was given. The infant became oedematous, acidotic, with low serum sodium and high potassium levels, and died at 57 days.

OTHER INVESTIGATIONS. Details of the biochemical investigations are given in Table 1. A radiograph of the epiphyses taken after death showed no evidence of premature ossification of the carpal bones. The urinary ketosteroid level was not estimated owing to the great technical difficulty of obtaining a 24-hour specimen of urine.

The mother's urinary 17-ketosteroid output (estimated in January, 1950) was 12·1 mg./24 hours. She is now pregnant again and we intend to do serial estimations during this pregnancy.

POST-MORTEM REPORT. Both adrenal glands occupied their normal position and were considerably enlarged (Fig. 4). The right gland weighed 6·0 g. and the left 5·5 g., their combined weight being 49% of the combined weight of the kidneys. Each gland was firm and uniformly grey in colour. The surface showed numerous fine corrugations together

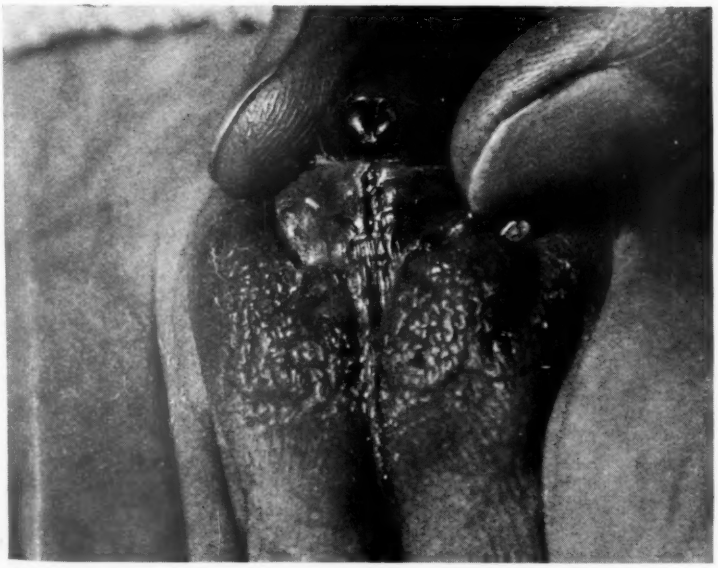

FIG. 2.—Photograph (Case 1) showing corrugated labia resembling scrotal sacs, central median raphe, urethral orifice at base of enlarged clitoris, and blind dimple, resembling urethral orifice, at tip of clitoris.

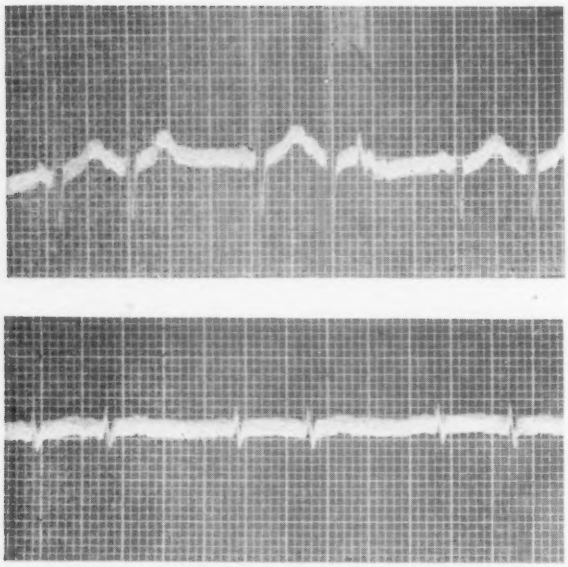

FIG. 3.—Electrocardiogram at 45 days showing coupling due to alternate auricular extra-systoles. (Leads I and CR IV only taken.)

with many small, round, pale nodules which projected above the general surface and measured up to 2 mm. in diameter. On the cut surface the cortex showed prominent, duplicated convolutions and had an average thickness of 3-4 mm. The medulla was mildly congested.

The thin, atrophic thymus weighed only 1·0 g. The uterus (2·5 cm. long) and the Fallopian tubes (2 mm. in diameter) were normal in size and configuration (Fig. 5) but the vagina opened on to the posterior wall of the urethra 1·0 cm. above its external orifice by an aperture only 1 mm. in diameter. The right ovary measured 2·2 × 0·3 × 0·2 cm. and the left ovary 1·7 × 0·3 × 0·1 cm. Although of normal length both were thinner than normal. Dorsal to the outer end of each ovary was a small, round nodule of adrenal tissue measuring 0·4 cm. in diameter. There was no obvious prostate gland.

The foramen ovale of the heart was wide, but all other organs appeared normal.

MICROSCOPY. The entire adrenal cortex (Fig. 6) was three to four times its normal thickness. The glomerular zone was thin and ill-defined and only in a few areas could a definite pseudoglandular arrangement of the cells be seen. Where present it was composed of cells with uniform round vesicular nuclei and slightly eosinophilic cytoplasm. In many places the glomerular zone was completely absent and here the columns of the fascicular zone tended to spread in rows lying parallel to the capsule. Although small islands of cortical tissue were present in the capsule there was no evidence of direct extension of the parenchyma through the capsule itself. Deep to the zona glomerulosa, and in places abutting on the capsule, was a thin, continuous layer of cells arranged mainly in columns at right angles to the surface and representing the zona fasciculata. These cells were regular in size and possessed vesicular nuclei and a finely granular, slightly eosinophilic cytoplasm.

The arrangement of the cells in the next and thickest zone varied in different parts of the gland. In some areas they were arranged in long parallel columns continuous with those of the fascicular zone, but elsewhere they had a reticular formation. Whatever the pattern, the component cells were the same. Three cell types could be identified. The majority resembled those of the more superficial cortex, but their cytoplasm was more eosinophilic and contained granules which were faintly stained by the Ponceau-fuchsin technique. Amongst these were many cells with vesicular nuclei, prominent nucleoli, and vacuolated cytoplasm containing coarse fuchsinophil granules. Finally there were scattered cells with dense nuclei and deeply eosinophilic cytoplasm similar to those found in the adult type of reticular cortex. These cells were more numerous in the outer part of the reticular zone, and it was here that the greatest fuchsinophilia was found. No pigment was present. In the deepest part of the cortex was a layer, 2-3 cells in thickness, representing the prenatal reticular cortex undergoing normal involution. Its cells were

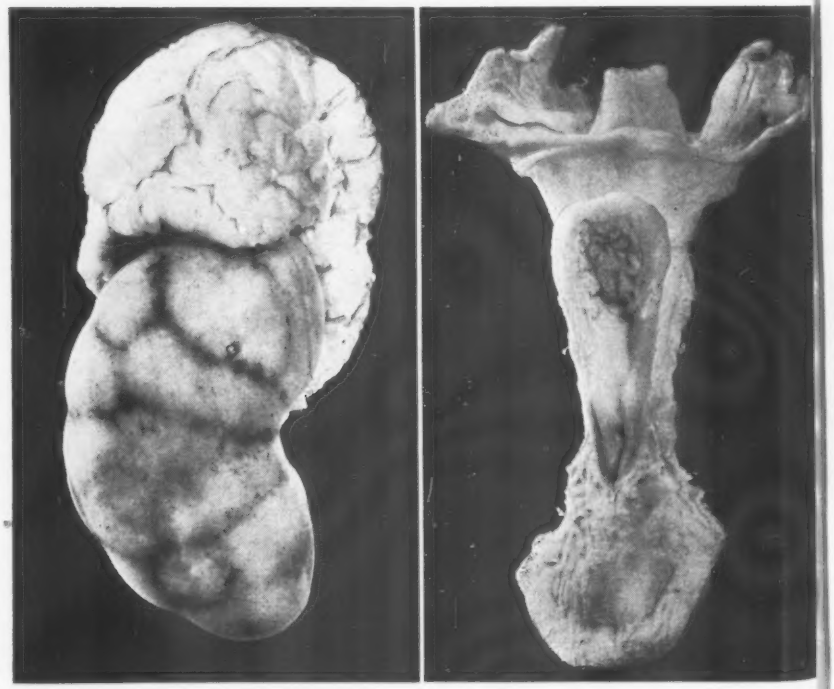

FIG. 4.—Right adrenal (Case 1) showing convolutions of surface.

FIG. 5.—Internal genital organs (Case 1) showing opening of vagina into urethra.

typical and quite distinct from those in the more superficial, adult type of reticular zone. The structure of the adrenal rests was identical to that of the adrenal cortex proper. The thymus gland showed crowding of the Hassall corpuscles, many of which were greatly enlarged and degenerate.

Sections of the pituitary gland were stained by Mann's methyl-blue-eosin technique and the cells counted in every third field of every third line. A differential cell count gave basophils 30·5%; eosinophils 14·8%; chromophobe 54·7% (total cells counted 16,230).

All other organs were normal.

Case 2 (C.R.). This infant (who was not seen by either of us during life) was born on August 9, 1948. Birth weight was 8 lb. 4 oz. (3,747 g.). She was the second child of healthy parents, the first being a normal boy. The external genitalia more closely resembled those of a male than did those of case I, the urethra being in the position of penile hypospadias. Although no testes were palpable, the infant was thought to be a male. No abnormality of any other system was found. She started vomiting when 8 days old, and had in all four crises characterized by pyrexia, vomiting, and lethargy. The stools were sometimes loose, but occasionally constipated. In one crisis pinpoint pupils were noted. The crises were treated empirically with saline with good but temporary response. The urinary chlorides were estimated only twice (6 g. per litre at 73 days and 4 g. per litre at 108 days). Various diagnoses, including pyloric stenosis and gastro-enteritis, were considered, but the blood chemistry was not investigated and the infant died suddenly at 261 days, after she was apparently starting to do well.

POST-MORTEM Report. The right adrenal gland (Fig. 7) weighed 6·0 g. and the left 7·0 g., their combined weight being 33% of the combined weight of the kidneys. Their gross appearance was similar to that in Case I, but the hyperplasia and duplication of the cortex was more marked.

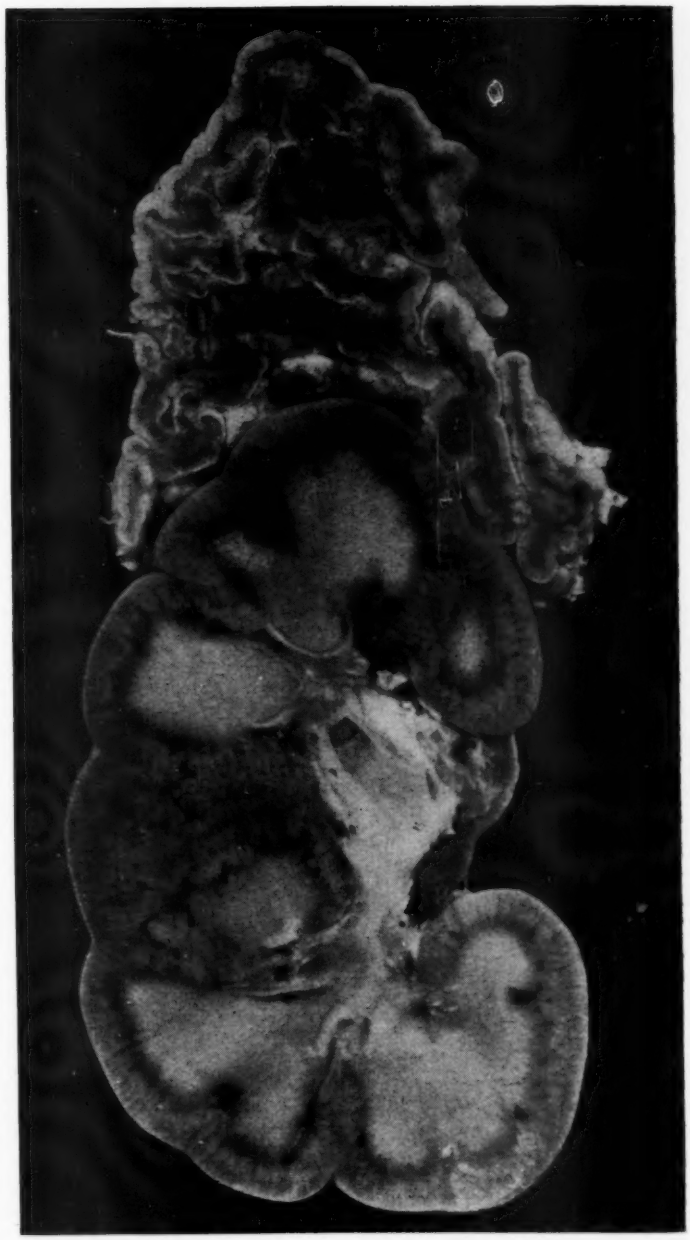

FIG. 7.—Right adrenal (Case 2) showing thickening and duplication of cortex. × 2.

The thymus gland (10·5 g.) appeared normal. Although the uterus (2·3 cm. in length) was of normal size, both Fallopian tubes were small with a diameter of less than 1 mm. The vagina, 1·3 cm. in length, had a diameter of 0·8 cm. at the cervix but rapidly narrowed and opened on to the posterior wall of the urethra by an

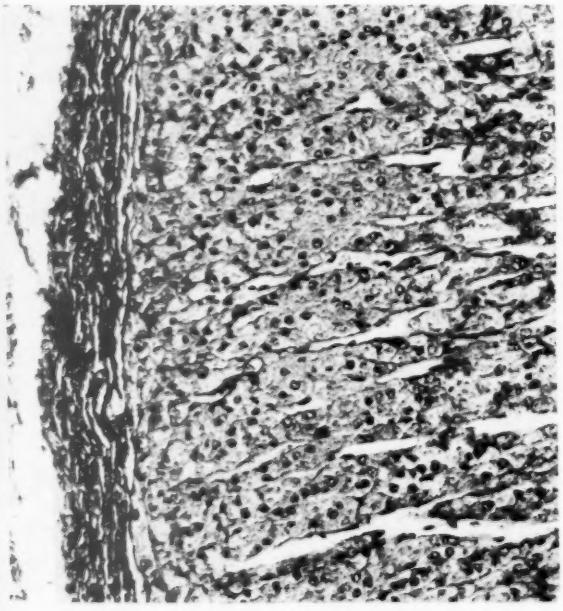

FIG. 6.—Adrenal cortex (Case 1) showing absence of zona glomerulosa and portion of hyperplastic zona reticularis. Ponceau-fuchsin × 165.

orifice measuring 1 mm. in diameter. Surrounding the upper parts of the urethra and vagina was a hard, pale mass of tissue which proved histologically to be prostatic tissue. The right ovary measured 2·0 × 0·7 × 0·3 cm. and the left ovary 1·9 × 0·6 × 0·3 cm. Lying in the right broad ligament between the Fallopian tube and the ovary were two adrenal rests each measuring 2 mm. in diameter.

MICROSCOPY. The adrenal cortex (Fig. 8) was about three times its normal thickness. The glomerular zone was thin and, although absent in a few places, it was much more obvious than in case I. In contrast, the fascicular zone was almost non-existent, the zona glomerulosa blending with the zona reticularis, which occupied about four-fifths of the total thickness of the cortex. In only a few areas were the cells of this zone arranged in parallel columns and even here the columns tended to anastomose. Only two types of cell could be distinguished. The greater number were of uniform size with vesicular nuclei and finely vacuolated, faintly eosinophilic cytoplasm. Here and there were smaller cells with denser nuclei and strongly eosinophilic cytoplasm in which vacuoles were less evident. These cells gave a strong fuchsinophil reaction. They were found in groups throughout the reticular zone, mainly in its superficial part. No pigment was present. There was no evidence of the foetal reticular cortex. The adrenal rests had a structure essentially the same as the cortex of the adrenals themselves.

A few Hassall corpuscles in the thymus gland were slightly enlarged and degenerate.

A differential cell count of the pituitary gland gave basophils 25·6%; eosinophils 13·9%; chromophobes 60·5% (total cells counted 18,623).

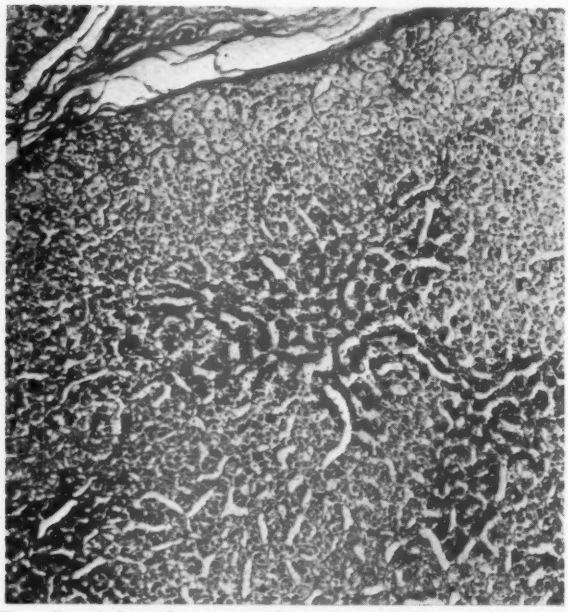

FIG. 8.—Adrenal cortex (Case 2) showing absence of zona fasciculata and groups of fuchsinophile staining cells in zona reticularis. Ponceau-fuchsin × 62.

Both kidneys showed numerous small areas of calcification, identified as calcium by staining by the von Kossa technique. These were chiefly in the interstitial tissue of the cortex and beneath the epithelium of the second convoluted tubules where they produced distortion of the lumina. A smaller number of rather larger deposits were also present in the outer part of the medulla in relation to both the collecting tubules and the loops of Henle. Here and there they appeared to have broken through the tubular epithelium and were lying in the lumen itself. There was no inflammatory fibrous or foreign body reaction around the calcium. A striking feature was the marked fatty change of the loops of Henle.

All other organs were normal.

Discussion

Diagnosis and Treatment. In a female pseudohermaphrodite, or in an infant with a previous family history of adrenal hyperplasia, it is relatively easy to bear in mind the possibility of adrenocortical insufficiency. In a male infant before any sexual changes have developed the diagnosis is more difficult. The most characteristic clinical signs are vomiting, lethargy, and sweating, usually of insidious onset. These symptoms are common to many neonatal diseases, but an outstanding feature is the degree of lethargy and anorexia. If these symptoms suddenly lead to a profound collapse associated with dehydration, a subnormal temperature or hyperpyrexia, sometimes pinpoint pupils and small mucoid stools, the possibility of an Addisonian crisis should be considered. If a normal or high urinary chloride level is present despite the previous vomiting, and if the crisis responds dramatically to saline therapy, with or without cortical extract, the diagnosis becomes even more probable. Biochemical studies are, however, essential to confirm the clinical impression, and in a crisis low serum sodium and chloride and high potassium levels will be found in the presence of a relatively high urinary output of sodium and chloride. The serum chemistry may alter very rapidly from day to day, as can be seen from Table 1, as also in cases of adrenocortical insufficiency from other causes. As in Addison's disease the serum sodium level is a much more sensitive guide to progress than the serum chlorides. One may expect similar but less marked biochemical changes in those cases where the progress of the disease is slow, as in our case 2. Clinical diagnosis of these is particularly difficult, but the presence of persistent vomiting and feeding difficulty with periods of dehydration and persistent failure to thrive should lead to investigation of the serum and urinary electrolyte levels on several occasions. Jaudon (1946) has suggested that

TABLE 1

ANALYSIS OF BIOCHEMICAL INVESTIGATIONS IN CASE 1

Age (Days)	Serum Levels				Other Investigations
	Na.	K	Cl.	HCO_3	*Urea*
	(*a*) m.eq./litre Normal 137–146 (*b*) (mg./100 ml.) (315–336)	(*a*) m.eq./litre Normal 4·6–5·6 (*b*) (mg./100 ml.) (18–22)	(*a*) m.eq./litre Normal 95–108 (*b*) (mg./100 ml.) (555–630)	(*a*) m.eq./litre Normal 19–30 (*b*) Vol.% CO_2 (40–60)	mg./100 ml.
6	140·5 (323)		102·7 (600)	30 (60)	26
19	131·7 (303)		109·1 (638)		
20	131·7 (303)	5·79 (22·6)	106·1 (620)		*Urine* Cl. 7 g. per litre.
30	98·26 (226)		92·43 (540)		*Urine* Cl. 4 g. per litre.
37					24 hour collection. *Urine* Na. 114·8 m.eq./litre. (264 mg./100 ml.) Cl. 154·0 m. eq./litre. (900 mg./100 ml.).
38	146·1 (336)		99·61 (582)		61
40	114·4 (263)		94·48 (552)		*Urine* (4 hour collection). Na. 93·93 m. eq./litre. (216 mg./100 ml.). Cl. 102·7 m. eq./litre. (640 mg./100 ml.). Urea 1·8 mg./100 ml.
41		9·743 (38·0)	95·68 (559)		
42		9·230 (36·0)			
43		9·101 (35·5)	131·6 (769)	13·1 (26·2)	
44	140·9 (324)	5·382 (21·0)	108·1 (632)	27·7 (55·5)	52 Hb. 60%.
45			105·3 (615)		Hb. 60%.
47	136·6 (314)		108·5 (634)	22·15 (44·3)	61 (3 hours after feed.) Sugar 75 mg. %.
48		6·153 (24·0)			
50	122·6 (282)	7·333 (28·6)	106·1 (620)	17·5 (35·0)	77 (3 hours after feed.) Bl. sugar. 70 mg. %. Hb. 65%.
51	193·6 (321)		107·8 (630)		60
52	131·7 (303)	10·79 (42·1)	107·5 (628)	17·35 (34·7)	
53	134·8 (310)		103·9 (607)	25·0 (50)	
54	137·4 (316)		104·9 (613)		Hb. 72%. Serum Proteins. 6·04 g./100 ml.
55	134·0 (308)		107·4 (627)		34
56	110·4 (254)		104·2 (609)	10·5 (21)	Bl. Sugar 56 mg. %. Hb. 62%.

temporary adreno-cortical insufficiency in infancy may be an important cause of poor general progress, and may not always be associated with adrenal hyperplasia. This is an interesting possibility which requires further investigation.

Once diagnostic proof of adreno-cortical insufficiency has been provided by the blood chemistry, maintenance therapy should be attempted. Some patients can undoubtedly be kept alive with small or irregular quantities of saline, as in our second case, and in the patient of Wilkins *et al.* (1940) who had a 'craving for salt' and survived without therapy until 3 years of age. Others require a large regular intake of saline, e.g., Darrow's case (1943-4), which received 3 g. NaCl. daily before becoming stabilized satisfactorily. Opinions seem divided on whether to give some of the sodium as molar lactate or bicarbonate. This is probably unnecessary except in a crisis, when there is a danger of producing hyperchloraemic acidosis with saline alone. A similar finding is reported by Zuelzer and Blum in their (1949) case II. Cortical extract should certainly be given in a crisis. Although the dose does not appear to be established, by analogy with cases of Addison's disease, it is probably preferable to use crude cortical extract rather than percortin in a dosage containing at least 2-4 mg. a day of DOCA. This dosage can be reduced after 24 hours and the necessary maintenance dose found by trial and error. Some of these cases have been well stabilized by DOCA implants (Darrow, 1943-4) and others. The dangers of DOCA therapy are stressed by Jacobsen *et al.* (1949) and by Darrow (1943-4) who produced a crisis by giving DOCA without saline. The latter comments on the risk of producing cardiac symptoms and cardiac enlargement in adults with Addison's disease receiving DOCA therapy. In case 1 cardiac irregularity was a striking feature and there was an inconstant systolic murmur. In view of the known capacity of DOCA to produce myocardial damage, and even necrosis, it is possible that these symptoms were due to treatment, although 'slow' or 'irregular' cardiac action has been recorded in cases which have received no treatment (Dijkhuizen and Behr's case 4, 1940; Zuelzer and Blum's case 4, 1949). It therefore seems possible that the cardiac irregularity was due to the toxic effects of the high serum potassium, although auricular extra-systoles are not apparently common in adults in Addisonian crises.

There is at present no known method of counteracting the effects of the excessive sex hormones, and virilism progresses. As yet no case of a female pseudohermaphrodite with Addisonian crises has been recorded as surviving beyond infancy, all the cases successfully treated being males (Butler *et al.*, 1939; Thelander and Choffin, 1941; Jacobsen *et al.*, 1949; Darrow, 1943-4). Jacobsen and his colleagues discuss the potential difficulties of later treatment of these cases as they approach puberty.

Correlation of Clinical and Histological Findings. Despite the occasional arrangement of the cells in parallel columns in our two cases, there was no doubt that the cells composing the hyperplastic zone corresponded to those of adult reticular tissue. In addition, however, large vacuolated fuchsinophil cells were diffusely scattered throughout the reticular zone of case 1 and large groups of fuchsinophil cells were present in case 2. It was observed that those cells showing the most marked fuchsinophil reaction were also the most deeply stained with eosin. It appears unlikely that the whole of the adult reticular tissue was produced after birth and, as normally involuting foetal cortex was present in the first case, it is probable that both adult and foetal types coexisted during intra-uterine life.

The marked thinning of the glomerular zone in case 1 and its less marked deficiency in case 2, where it was associated with almost complete absence of the zona fasciculata, suggest that this was related to the Addisonian attacks, especially in view of the fact that the first case was the more severe. However, the great increase in the surface area of the gland with the duplication of the layers of the cortex may, by spreading the zona glomerulosa, give a false impression of deficiency of that layer.

The significance of the renal changes in case 2 is difficult to assess. The salt-water hormone of the adrenal is thought to act chiefly by influencing electrolyte reabsorption in the loops of Henle. It is therefore a tempting hypothesis that deficiency of this hormone caused the fatty changes and calcification found in this area in case 2. If this were so, however, one would expect similar findings in other cases and in Addison's disease in adults, whereas renal changes in Addison's disease are inconstant. Detailed histology of the kidneys has been reported in very few cases of the adrenogenital syndrome, and we have been unable to find any record of similar changes.

We thought it might be of interest to tabulate (Table 2) the chief clinical and histological findings in our two cases, as they appear to represent two clinical types of adreno-cortical insufficiency, case 1 being fulminating and case 2 subacute.

Summary

Two female pseudo-hermaphrodites due to bilateral adrenal hyperplasia are reported. The first case had severe Addisonian crises, biochemically

TABLE 2

COMPARISON OF CLINICAL AND HISTOLOGICAL FINDINGS IN CASES 1 AND 2

Case 1	Case 2
Frequent severe Addisonian crises requiring treatment with DOCA and saline.	Less frequent 'crises' (biochemically not confirmed) responding to saline alone.
Extra saline essential from 1st week of life.	Period of fair growth without saline.
Macroscopically: adrenal hyperplasia (6·0 and 5·5 g.).	Adrenal hyperplasia (6·0 and 7·0 g.).
Microscopically: zona glomerulosa grossly deficient, zona fasciculata normal, zona reticularis adult type. Diffuse fuchsinophil staining and vacuolation.	Zona glomerulosa moderately deficient, zona fasciculata grossly deficient, zona reticularis with groups of fuchsinophil cells. No abnormal vacuolation.
Kidneys normal.	Kidneys showed calcium deposits in tubules and fatty change in loops of Henle.

confirmed, but the second followed a more prolonged and less severe course. The evidence that the clinical differences between the two are associated with differences in the histological findings is presented. The possible significance of the recurrent cardiac irregularity in case 1, and the histological changes in the renal tubules in case 2, are discussed, and other cases of adreno-cortical insufficiency due to adrenal hyperplasia found in the literature are mentioned.

We should like to thank Dr. Helen Mackay and Dr. Ian M. Anderson for permission to publish these cases and for their kind advice and encouragement. We are also grateful to Dr. Winifred Young and Dr. B. Levin for their stimulus and advice. Dr. D. P. King performed the necropsy on case 2 and kindly allowed us to use material for photographs and sections. The biochemical investigations on Case 1 were done by Mr. T. P. Whitehead, A.R.I.C., and the histological preparations of both cases by Miss F. Humphries, A.I.M.L.T., and we wish to thank them both.

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ENTEROGENOUS CYST CAUSING CONGENITAL INTESTINAL OBSTRUCTION

BY

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Cysts whose walls reproduce completely or incompletely the structure of gut, whether discovered in the wall of the gut, attached to the gut, or even more or less remote from the gut, must have been derived from the gut (Evans, 1929). They originate either in the vitello-intestinal tract or in diverticula normally found in the developing embryonal entoderm (Lewis and Thyng, 1908). One or more of these diverticula may persist as diverticula and increase in size, or they may become closed off from the bowel and form separate cystic structures. They have been found and described in all parts of the alimentary tract from the oesophagus to the sigmoid colon. The commonest site is in relation to the small intestine, with the ileo-caecal angle and the duodenum as the next most common sites.

Most of these cysts, when they occur in infancy and childhood, have been found incidentally during post-mortem examinations.

In looking through the literature it appears that no case has been found of a cyst being the cause of congenital intestinal obstruction. In adults the cysts present clinically as simple abdominal tumours or as a result of complications. The complications which have been described are (1) intestinal obstruction including pressure, volvulus, intussusception, carcinoma; (2) inflammation, acute and chronic (tuberculous condition of a cyst and related bowel); and (3) neoplastic conditions which may be primary in the cyst or secondary from direct spread from related bowel.

The case reported showed an enterogenous cyst in the upper jejunum causing congenital intestinal obstruction with a second large cyst in the lower ileum.

Case Report

A boy, weighing 9 lb. 6 oz., was born at 10.30 p.m. on July 20, 1949. The mother had marked hydramnios; otherwise the pregnancy and parturition were normal. The baby was cyanosed at birth, had distension of the abdomen, vomited liquor and vernix, but had no bowel action in the first few hours after birth.

On examination 15 hours after birth the baby showed normal development. There was slight dusky cyanosis, and numerous petechiae of the head and neck were noted. The fontanelles were normal, and also the chest and cardiovascular system.

Marked distension was present in the abdomen. A visible and palpable cylindrical mass, almost filling the whole abdomen and extending more or less transversely across it, was found and thought to be distended colon. There were no bowel sounds on auscultation. The little finger could be inserted about 1½ in. into the rectum when there appeared to be some narrowing. A clinical diagnosis of intestinal obstruction probably due to large bowel obstruction, was made.

A straight x-ray film was taken of the abdomen with a metal probe in the rectum. The film showed gas in the upper abdomen only, corresponding roughly to the stomach and duodenum. There was no gas in the rest of the abdomen.

A laparotomy was performed as the clinical picture of obstruction with distension suggested a colonic or rectal lesion, although the radiograph showed gas in the upper abdomen only.

Pre-operative treatment included aspiration of the stomach, and the administration of penicillin (30,000 units), vitamin K (10 mg.), and DOCA (2 mg.).

Fig. 1.—Cyst at lower end of ileum with catheter passed through lumen of ileum.

Operation on July 21, 1949, was performed under continuous ether vapour and oxygen, and a right paramedian incision was employed.

A large cylindrical cyst, about 12 in. long, filling the central abdomen was found, extending to within 6 in. of the ileo-caecal junction (Fig. 1). The cyst was tense and lying between the two layers of the mesentery with the ileum stretched over its outer surface. The mesentery was oedematous, congested, with petechial haemorrhages, suggesting that there had been some partial volvulus of the involved region. A second cyst, containing 40 ml. of fluid, was found 8 in. from the duodeno-jejunal flexure. This cyst had twisted together with the jejunum *in utero*, and, on untwisting, an area of complete atresia (1½-2 in.) of the jejunum was found. This appeared as a fibrous cord connecting two parts of the jejunum. The remainder of the abdominal organs appeared normal.

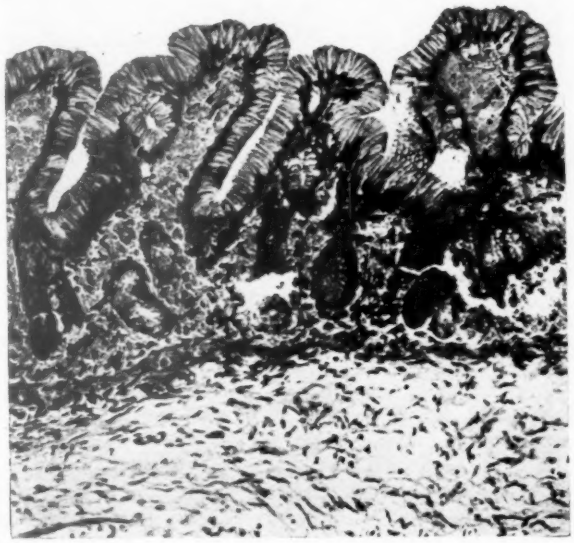

FIG. 2.—Section showing columnar mucus-secreting epithelium lining the cyst. × 140.

A section 12 in. long of lower ileum and cyst were resected and anastomosis performed. A side-to-side anastomosis of the jejunum, short circuiting the cyst and the atretic portion, was performed. The cyst was aspirated and partially excised, the edges being oversewn. The wound was closed without drainage.

Continuous oxygen was instituted immediately after operation, and 30 ml. of saline given subcutaneously every four hours. Penicillin, 150,000 units, was given twice daily.

The baby improved for the first two days, and normal bowel actions occurred. On the third day the abdomen became distended and some flatus and meconium were passed following a rectal wash-out. But the infant's general condition gradually deteriorated in spite of treatment, and he died on July 26, 1949.

Post-mortem Examination. The heart and chest were normal apart from small foci of consolidation in the lungs.

Some peritonitis was present in the abdomen with a small pocket of pus near the anastomosis of the lower ileum. Inspection showed thrombosis of the mesentery in this region, with an area of necrosis in the mesenteric border of the anastomosis and leakage from the ileum.

The liver was enlarged and bile-stained.

The cyst wall showed a lining of a thin layer of mucus-secreting tall columnar epithelium (Fig. 2), possessing shallow crypts. The remainder of the wall showed a thin submucous layer and three well defined muscle layers. The whole cyst showed all the main elements of bowel histology thereby proving its origin.

Summary

A case of congenital intestinal obstruction due to intra-uterine volvulus of an enterogenous cyst in the jejunum, with a second large cyst in the lower ileum, has been described. No other record of a cyst causing congenital obstruction has been found in the literature.

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HAEMOPOIESIS AND SIDEROSIS IN THE FOETUS AND NEWBORN

BY

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In 1941 Gilmour described haemopoiesis in the foetus and newly born infant. His investigations were primarily qualitative and were undertaken as a preliminary to the study of erythroblastosis foetalis (1944). The investigations to be reported here were essentially quantitative. Their ultimate objective was the comparison of the amounts of haemopoietic tissue and stainable free iron in the organs of newborn infants dying of haemolytic disease with those of a control group of infants dying from other causes. The observations on the control group of infants seemed so interesting and the conclusions so important that they are reported here in detail.

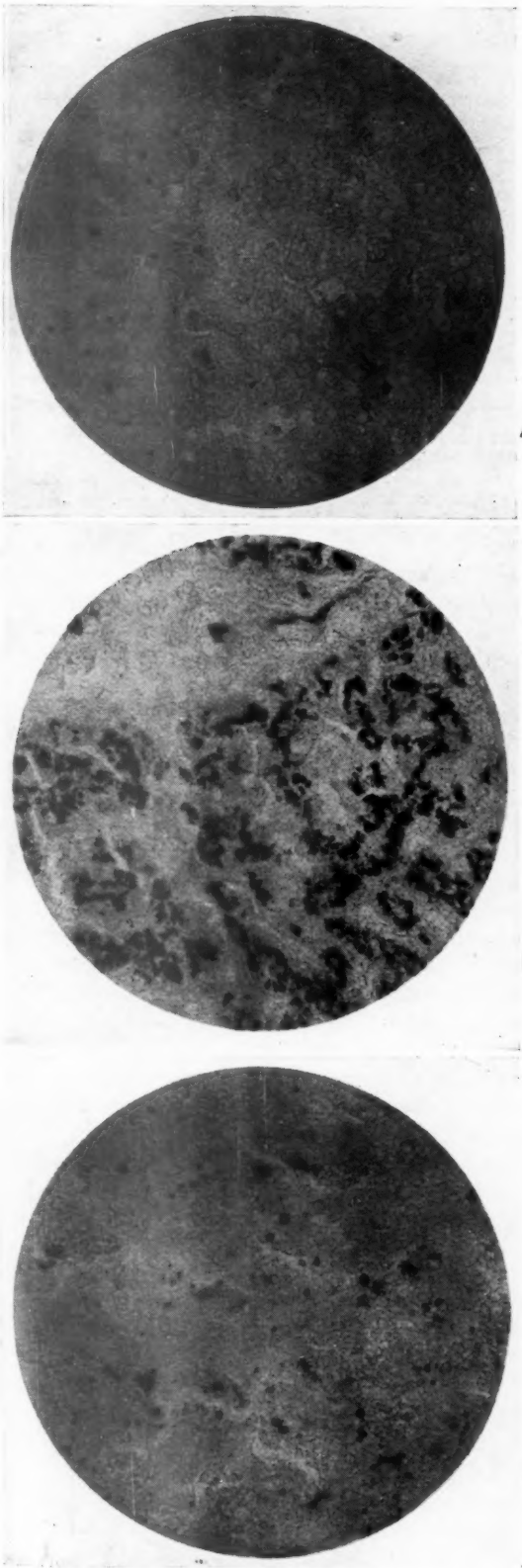
It is shown below that recession of hepatic haemopoiesis is of two types: a foetal type occurring mainly in the last few weeks of intra-uterine life and an infantile type which follows approximately a logarithmic law. The mechanisms concerned in these two types are probably different. The postnatal fall in the erythrocyte count is due, at least in part, to the decline in extramedullary erythrocyte production rather than mainly to excessive breakdown of red cells. The rate of fall of the red cell count depends, therefore, on the rate of recession of extramedullary haemopoiesis before and after birth and on the mean life span of the cells. Free iron was found in the livers of half the stillborn infants examined; this corresponds to the high but variable iron content of the foetal liver reported by Ramage, Sheldon, and Sheldon (1933), and by McDougall (1946). It suggests that this is a store of iron available for hepatic haemopoiesis. After birth hepatic siderosis increased in frequency and amount as extramedullary haemopoiesis diminished, which might be expected with a reduced local utilization of iron.

On examining the results of previous workers with regard to (1) the time of the greatest fall in the red cell count (Findlay, Higgins, and Stanier, 1947); (2) the occurrence of physiological icterus (Davidson, Merritt, and Weech, 1941; Findlay *et al.*, 1947); (3) experimental bilirubinaemia following life at low oxygen tensions (Goldbloom and Gottlieb, 1930); and (4) hepatic siderosis (Brückmann and Zondek, 1939), it is evident that the theory of excessive haemolysis after birth as the cause of the postnatal fall in the red cell count is inadequate. Thus the way is opened for a reconsideration of the changes in the haemopoietic system at birth.

Material and Methods

Selection of Material. The livers, spleens and kidneys of 18 stillborn and 74 live born infants were examined. The live born infants died at ages ranging from 10 minutes to 7 months. Forty-eight infants were premature and 44 full term. The material was drawn from a pool of about 1,000 infant necropsies performed by myself. The selection was not random but drawn so as to resemble the series of cases of haemolytic disease with regard to the size of the various age groups and the degree of maturity. Since all these infants were dead they did not constitute a group of strictly normal controls, an unavoidable limitation in this kind of investigation. Almost all the premature infants of 3 days of age or less died as a result of intracranial birth injury, asphyxia, or atelectasis; after three days infection caused the majority of deaths. In the full term infants intracranial birth injury, asphyxia, or atelectasis accounted for most of the deaths in the first week of life, after which infection was the principal cause of death. I have, perforce, assumed that these lesions caused no significant general change in haemopoiesis or iron metabolism in this group of infants, although some change may have occurred in individual cases. Since the pool was collected over the years 1941 to 1948 no systematic investigation of the Rh factor had been made on most of the infants. There was no clinical or pathological evidence that any of these infants had haemolytic disease of the newly born, although in two cases subsequent sibs were affected.

The degree of prematurity was determined principally by the menstrual history of the mother. In the analysis which follows crown-heel length was sometimes used as a second criterion. These measures were used in preference to body weight, since in this analysis the emphasis was on anatomical maturity rather than on functional capacity, which clinically is so important. Moreover in



haemolytic disease the body weight may be increased by oedema. The assessment of prematurity is discussed by Potter and Adair (1940), and the procedure adopted here is in line with their findings.

Technique. Sections of the liver, spleen, and kidney were stained by Mayer's haemalum and eosin and Gömöri's iron stain (1936). For the iron reaction watery eosin was used as a light counter stain for the purpose of contrast. Occasionally carmalum was also used but this produced a picture too full of detail for estimating the amount of iron present. Sections of the liver and spleen were also stained by Van Gieson's method and by Gömöri's (1937) silver method for reticulin.

Hepatic haemopoiesis was measured by counting the number of foci of haemopoiesis in a hundred microscopic fields ($\times 275$) and taking the mean. When the foci were few they were usually small and discrete; when numerous they were usually larger and more confluent making it difficult to count them accurately. Siderosis was estimated by examining a hundred fields ($\times 275$), and if no iron was seen a score of zero was given; if a very little iron, a score of one; if the field was packed with iron to saturation a score of three; intermediate amounts were scored two. Fig. 1 illustrates this method of scoring. The number of fields for each score was thus found and the result expressed: for example, 0, 5, 75, 20, the score being in ascending order (0, 1, 2, 3) from left to right. The cases were then ranked according to their score formulae. Thus A, with a formula 20, 60, 20, 0, evidently contained less iron than B with a formula 0, 5, 75, 20. When formulae were so similar that no certain difference could be made (e.g., 0, 7, 72, 21, and 0, 5, 75, 20) they were given the same grade. It was found possible to divide the livers into 21 grades and the spleens into twelve.

Analysis of Results

Intra-uterine Recession. In Table 1 the number of haemopoietic foci present in the liver of stillborn premature infants is compared with the number found in stillborn full term infants. Whatever the criterion of prematurity, menstrual age, crown-heel length or both, the mean number of haemopoietic foci in premature infants exceeded that of full term infants. (When prematurity was determined by menstrual age alone or by both criteria taken together the difference was significant. When crown-heel length was used alone the difference was suggestive but not significant. When both criteria were used three infants were omitted since each was

(*A*) Iron visible as black dots in a few cells, score 1.

(*B*) Iron present in large amounts in almost all parenchymal cells, score 3. The iron-free patch corresponds to a small portal tract. From full term infant aged 3 days.

(*C*) Iron present in some liver cells, intermediate in amount between that seen in (*A*) and (*B*), thus score 2.

FIG. 1.—Three sections of liver showing the method of grading the visible iron content. The iron is stained by the Prussian-blue method; the rest of the tissue is stained lightly with eosin. Magnification $\times 275$.

TABLE 1

COMPARISON OF HEPATIC HAEMOPOIESIS IN STILLBORN INFANTS BORN PREMATURELY AND AT FULL TERM

	Comparison by Menstrual Age		Comparison by Crown-Heel Length*		Comparison by both Criteria	
	No. of Infants	No. of Foci of Haemopoiesis	No. of Infants	No. of Foci of Haemopoiesis	No. of Infants	No. of Foci of Haemopoiesis
Premature ..	7	4·91	6	4·07	10	4·84
Full term ..	11	0·92	12	1·67	5	0·99
Difference ..		3·99		2·40		3·85
t ..		4·63		1·96		3·98
P* ..		less than 0·001		lies between 0·1 and 0·05		lies between 0·01 and 0·001

* If the infant's crown-heel length is less than 50 cm. it is considered premature.
P is the probability that the full term and premature infants belong to the same group. When P is less than 0·05 the groups were considered to differ significantly, when P is less than 0·10 a suggestive difference was thought to exist.

premature by one criterion alone.) It follows that the main fall in haemopoietic activity occurred in the interval between the two groups, namely between the thirty-eighth and fortieth weeks of gestation.

None of the premature infants exceeded 38 weeks' gestation nor, when using both criteria, the corresponding crown-heel length of 48 cm. Table 2 shows that there was no relationship between the amount of haemopoietic tissue and the degree of prematurity. Hence two groups showed no merging with respect to the number of haemopoietic foci in the liver. The difference between the premature and the full term foetuses was clear-cut. This is perhaps a little surprising in view of variability in the duration of pregnancy. Thus Karn (1947) has shown the mean duration to be 280 days with a standard deviation of 11·3 days.

Postnatal Recession. Following birth the changes in haemopoiesis showed two phases. During the first two or three days of life the number of foci did not diminish, and indeed in the first 12 hours they often increased, though the increase was not statistically significant. After this period the phase of decline set in and the haemopoiesis rapidly disappeared. The decline in haemopoiesis with respect to age can be represented by a logarithmic function. Fig. 2 shows the curve for the full term infants; those for the other groups of infants two to eight weeks premature and more than eight weeks premature were similar. The mean number of foci for each age group is also plotted on the graph.

After the first three days the fit between the calculated line and the mean was very good, although there was a fairly extensive variation about the mean. The fit was also good for the premature groups. This curve clearly shows the two phases in postnatal hepatic haemopoietic recession. In the first two or three days the number of foci present fell below the calculated curve, but with a tendency to increase just after birth.

The point at which the curve cut the axis of time gave the mean time of disappearance of haemopoietic tissue from the liver. In full term infants the mean time of disappearance was about eight days, in infants two to eight weeks premature about 18 days, and in infants more than eight weeks

TABLE 2

COMPARISON OF THE AMOUNT OF HEPATIC HAEMOPOIESIS WITH THE DEGREE OF PREMATURITY, BY RANK CORRELATION (KENDALL)

(*a*) *By menstrual age*

Case No.	202	664	282	385	588	614	360
Rank of menstrual age*	1	2	3	4	5	6	7
Rank of no. of haemopoietic foci† ..	1	7	6	2	4	5	3

Coefficient of rank correlation=0.

(*b*) *By crown-heel length*

Case No.	664	282	202	385	588	367
Rank of crown-heel length*	1	2	3	4	5	6
Rank of haemopoietic foci†	5	4	1	2	3	6

Coefficient (not significant) of rank correlation=0·015.

† In ascending order.
* In descending order.

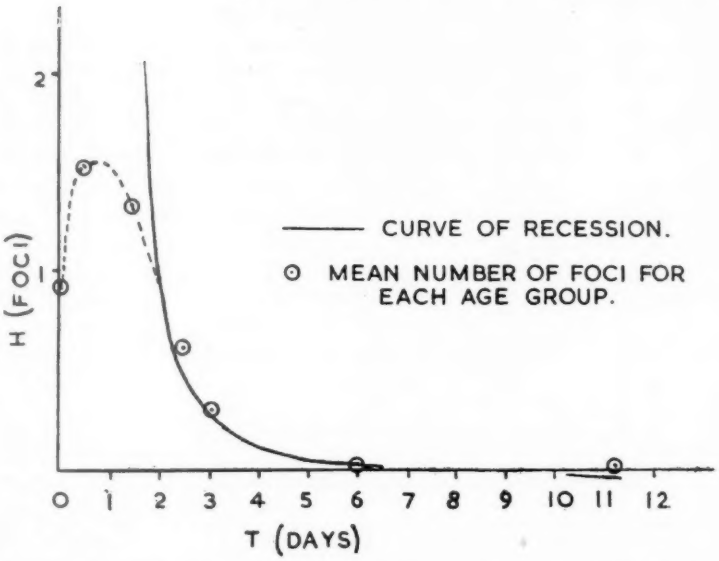


FIG. 2.—This shows the diminution in hepatic haemopoietic tissue with age at death (T), in the group of full term infants. Haemopoietic tissue is measured by the average number (H) of haemopoietic foci present in 100 high power fields. The postnatal increase in haemopoiesis is clearly shown and the close agreement of observations, after the first three days, with the calculated curve of recession is evident.

premature about 38 days. It follows that haemopoietic foci disappeared from the liver sooner in full term than in premature infants, and the more premature the infant the longer the foci persisted, although in diminishing numbers. It may be that the duration of these haemopoietic foci depended on the initial level of haemopoiesis at birth. Since, however, there was no relationship, in the range considered, between the degree of prematurity and the level of haemopoiesis in stillborn infants such a hypothesis remains speculative.

The haemopoietic foci lay in the liver sinusoids or in lacunae off them and also in the connective tissue of the smaller portal tracts. There was no evidence that the sinusoidal foci disappeared at a different rate from those in the portal tracts. No attempt was made to follow the changes qualitatively. When the foci were small and scanty the nuclei of the cells were highly pyknotic and some showed karyorrhexis. The cells were then difficult to distinguish from polymorphic leucocytes.

Two Types of Haemopoietic Recession. In Table 3 the mean time of disappearance of hepatic haemopoiesis in premature infants is compared with the mean time at which haemopoiesis would have been expected to disappear had the infant been born at full term. It follows that in infants two to eight weeks premature haemopoiesis disappeared on an average 17 days before the expected date of delivery, and in infants more than eight weeks premature it disappeared about 36 days before the expected date of delivery. In contrast, all of the full term infants, who were stillborn or survived up to two days (23 infants in all), had haemopoietic foci in the liver. It follows that in premature infants hepatic haemopoiesis recedes more rapidly after birth than if the infants continued to live *in utero*.

It was shown above, when considering the stillborn infants alone, that hepatic haemopoiesis diminishes in the last two weeks or so before birth. Hence two types of recession can be distinguished: (*a*) an intra-uterine type, and (*b*) an extra-uterine type, and the one process is not a simple continuation of the other.

In premature infants one or two rows of incompletely developed glomeruli may be seen beneath the capsule of the kidney; at term few infants have such immature glomeruli,and the extent of this immaturity is a useful guide in routine pathology to the degree of prematurity. This phenomenon has been extensively studied by Potter and Thierstein (1943). I found that postnatal maturation of the glomeruli of premature infants occurred at about the same time as if the infants had remained *in utero*. This is in contrast to the hastening of the haemopoietic recession which occurred in the same infants after birth.

TABLE 3

DEGREE OF PREMATURITY COMPARED WITH THE MEAN AGE OF DISAPPEARANCE OF HAEMOPOIETIC FOCI FROM THE LIVER

Degree of Prematurity	Full Term	2-8 Weeks Premature	More than 8 Weeks Premature
Mean degree of prematurity	0	35·0 days	73·5 days
Mean age when haemopoiesis disappears ..	8·0	18·0 days	37·6 days
Comparison ..	—	17·0 days	35·9 days

Time of Disappearance of Hepatic Haemopoietic Tissue. One of the objects of this investigation was to determine the time at which haemopoietic tissue disappeared from the liver. This clearly varied with the degree of prematurity and with the individual.

Hence the mean time of disappearance was an inadequate measure but, theoretically, limits could be set between which haemopoietic tissue would have disappeared in 95% of individuals. The method used was based on the work of Schultz (1930) using a formula of Snedecor (1946). The family of curves which represented the second phase of postnatal haemopoietic recession was given by the equation $\log_e (H+0{\cdot}01)=a+b \log_e T$. The 95% range for the time of disappearance of haemopoietic tissue is given in Table 4. Unfortunately the upper limit of this range was indeterminate for premature infants, probably due to inadequate data. This method of determining the range may seem a little artificial since the logarithmic formula is strictly a mathematical fiction. However, the conclusions drawn from the formula agreed with the observations. Thus of (*a*) full term infants, the first to show no foci was 3½ days old and the last 13 days old; (*b*) of infants two to eight weeks premature, the first to show no foci was 8 days old and the last 21 days old; (*c*) of infants more than eight weeks premature, the first to show no foci was 2 weeks old but the range was not long enough to give the final figure.

TABLE 4

95% RANGE FOR THE MEAN TIME OF DISAPPEARANCE OF HAEMOPOIETIC FOCI

	Mean Time (days)	RANGE (95%)	
		Lower Limi	Upper Limit
Full term	8·03	3·7	19·1
More than 2 weeks and up to 8 weeks premature	18·03	4·5	Indeterminate
More than 8 weeks and up to 18 weeks premature	37·6	12·4	Indeterminate

The Accumulation of Iron Pigment

Visible Iron in the Liver and Spleen of Stillborn Infants. Sections of tissue from 18 stillborn infants were studied. In nine infants there was a positive iron reaction in the liver and in six of these the reaction was also positive in the spleen. In one infant (S.360) iron was visible in the spleen but not in the liver. Statistical analysis showed no relationship between the presence or absence of visible iron in the liver and (*a*) the prematurity of the infant, or (*b*) the amount of hepatic haemopoietic tissue.

Relationship between Age and Visible Iron in the Liver. Fig. 3 shows the mean grade of visible iron in each age group plotted against the age at death. In both full-term and premature infants there was a fall in the visible iron content in the age range of 1 to 3 days, after which there was an almost progressive rise for 3 to 4 weeks, followed by a fall after about 3 months. Infants who were more than eight weeks premature were not included in the graph because the group was small and the individual variations so great that they upset the visual trend. However, all infants are included in Table 5. It can be seen that there was a higher

TABLE 5

FREQUENCY OF HEPATIC SIDEROSIS IN FULL TERM AND PREMATURE INFANTS

Age at Death	No. of Infants	No. with Siderosis
Stillborn	18	9
Less than 1 day ..	17	12
1< 3 days	10	3
3< 8 days	16	11
8<15 days	9	6
15<28 days	7	6
1<2 months ..	8	8
2 to 7 months ..	7	6
Total	92	61

proportion of infants without visible iron in the liver dying between one and three days than at any other period, and that after this the proportion of cases showing no iron rapidly diminished. There was much more individual variation with regard to visible iron than haemopoiesis. In all age groups, except the 1-2 months group, some livers gave a negative reaction for iron.

The fall in the visible iron (Fig. 3 and Table 5) in the early days of life was not statistically significant. It is interesting to note that the fall occurred one to two days later than the probable rise in haemopoiesis (Fig. 2). Although neither of those changes, taken separately, was significant they might have been when taken together. Unfortunately I know of no convenient test for combining them.

Comparison of Quantities of Haemopoietic Tissue and Visible Iron in the Liver. From Table 6 it can be seen that whereas siderosis was frequently associated with the presence of haemopoiesis it was

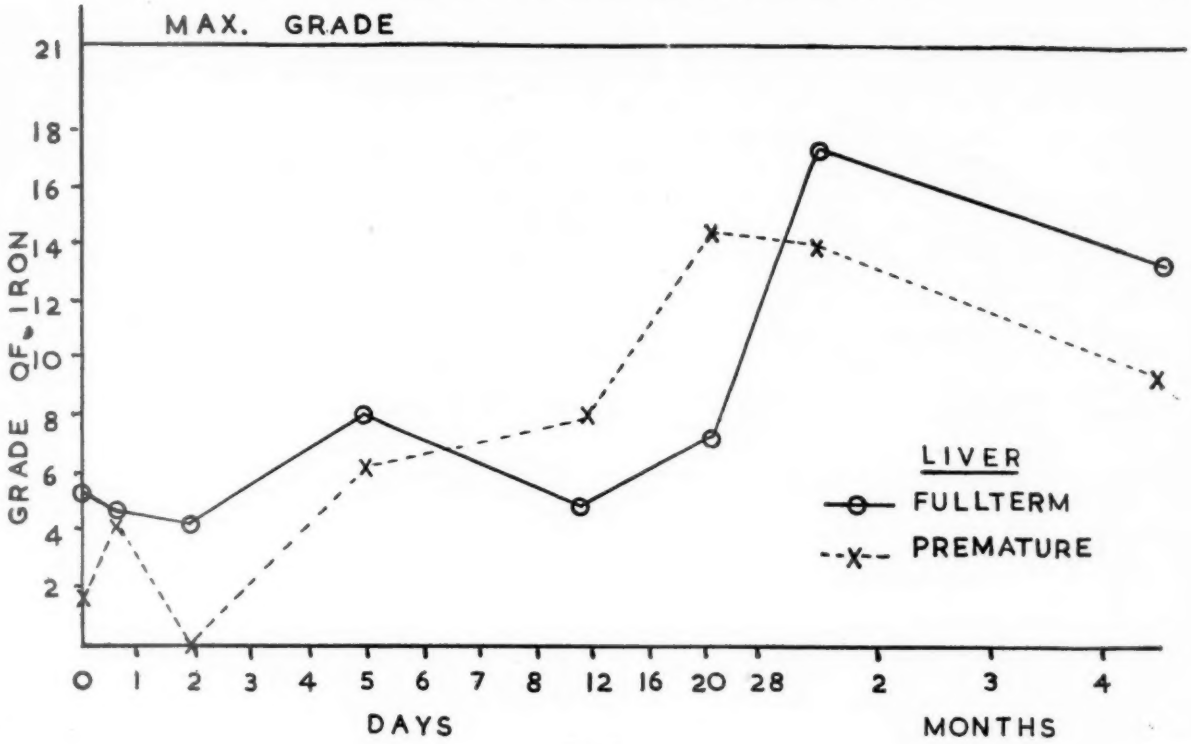


FIG. 3.

more frequently associated with its absence. The difference is statistically significant. Analysis of the data with regard to prematurity or other factors yields no further information.

TABLE 6

FREQUENCY OF HAEMOPOIESIS AND SIDEROSIS IN THE LIVER COMPARED

	No. with Haemopoiesis	No. without Haemopoiesis	Total
Siderosis present	34	27	61
Siderosis absent	25	4	29
Total ..	59	31	90

χ^2 (using Yates' correction) is 6·86 hence the distribution could occur by chance (Fisher and Yates, 1948) less than once in 200 times.

Distribution of Visible Iron in the Liver. Iron pigment was present in the liver cells, or in the cells in the sinuses, or usually in both. In only one infant (S.605) was the pigment present in the sinus cells and not in the parenchymal cells. The distribution of iron between sinuses and parenchyma bore no relation to the amount of pigment present or the age of the infant. In the liver cells the pigment was usually present as diffusely scattered granules but occasionally it was most marked near the bile canaliculi. Sometimes iron was visible in all the liver cells but, at others, it was concentrated in the cells near the portal tracts. Occasionally it was near the centrilobular veins. The distribution in the parenchyma bore no relationship to the amount of pigment present. Iron was found in the portal tracts themselves in only two livers, and then in very small amounts, which contrasts with some of my cases of haemolytic disease of the newly born in which this was a conspicuous feature. In the sinuses pigment was most often found in the Kupffer cells, but in nine livers it was also found in cells about the size of a red blood corpuscle. The nature of these cells was not determined. In the sinuses the pigment gave a diffuse coloration to the cells in contrast to the granular appearance of the liver.

Relationship between Age and Visible Iron in the Spleen. In Fig. 4 the mean grade of visible iron in the spleen in each age group is plotted against the age at death, and in Table 7 the number of spleens which contained iron in each age group are given. In the first few days after birth there was a fall in the mean amount of visible iron and in the frequency with which it was present. This fall was most marked in the age range 1 to 3 days. After this

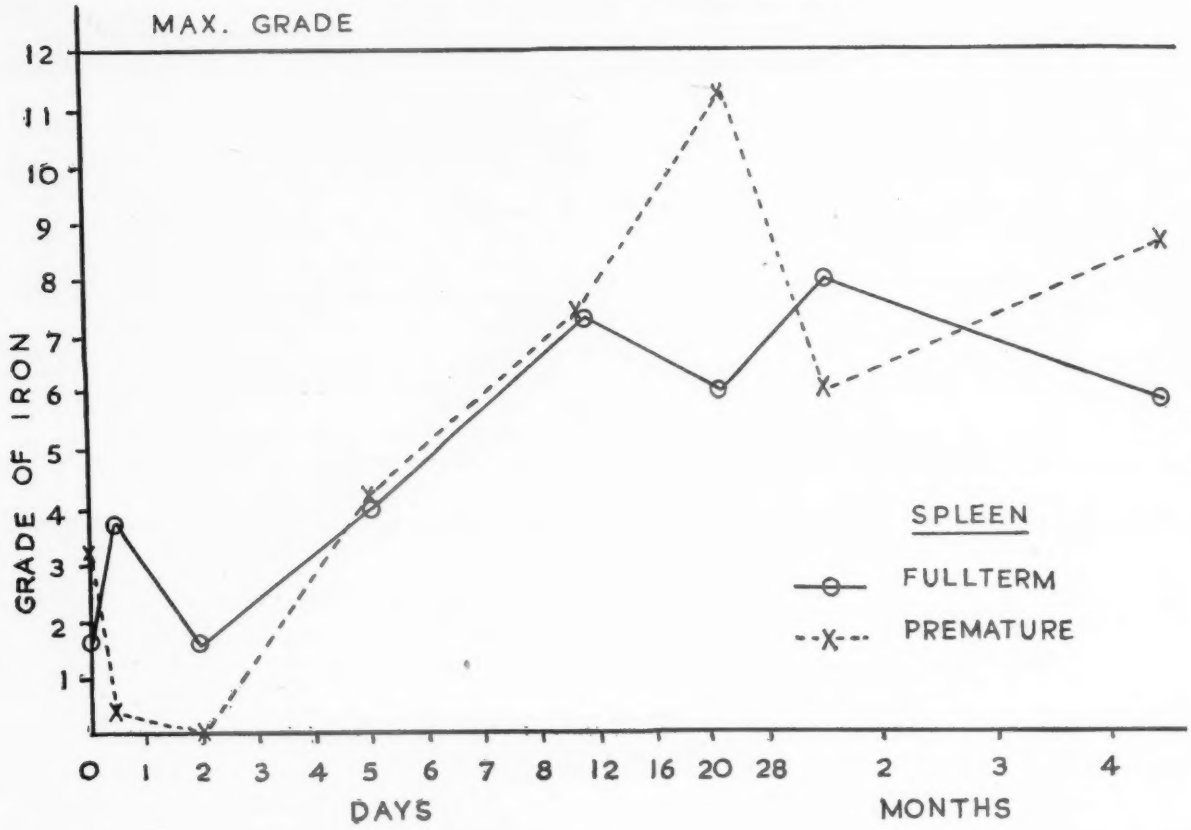


FIG. 4.

period the amount of iron progressively rose for one to two weeks and then varied about a maximum, but occasionally a spleen was found which showed no pigment. On inspection, there was no significant difference between the premature and full term group. The similarity in behaviour between the liver and the spleen was marked. The only easily detectable difference was that the maximum accumulation of iron occurred perhaps a little later in liver than in the spleen of full term infants, but this difference was not present in premature infants.

TABLE 7
FREQUENCY OF SPLENIC SIDEROSIS IN FULL TERM AND PREMATURE INFANTS

Age at Death	No. of Infants	No. with Siderosis
Stillborn	18	7
Less than 1 day ..	15	5
1< 3 days	9	1
3< 8 days	11	6
8<15 days	8	8
15<28 days	6	5
1 to 7 months ..	10	7
Total	77	39

Distribution of Iron in the Spleen. The siderotic granules were intracellular and were only present in the pulp, either in cells lining the sinuses or lying free in the sinuses. Neither the follicles nor the connective tissue of the capsule and trabeculae gave a positive prussian blue reaction. In haemolytic disease of the newly born the connective tissue frequently gives a positive iron reaction.

Correlation between Grades of Iron in the Liver and Spleen. The correlation coefficient was 0·555 and was statistically significant. This positive correlation, although rather low, is in conformity with the parallelism between the graphs showing the accumulation of the pigment with time (Figs. 3 and 4, and Tables 5 and 7).

Renal Siderosis. The kidneys of almost all these infants were examined. In only two cases was there

evidence of siderosis and in both it was very faint. This was in marked contrast to my series of infants with haemolytic disease of the newly born in which renal siderosis was conspicuous.

Results

The analysis may be summarized as follows:

(1) Hepatic haemopoiesis diminished in the later part of intra-uterine life, particularly in the last two weeks before the expected date of birth.

(2) In postnatal life haemopoietic tissue in the liver diminished after the second or third day of life. The process approximately followed a logarithmic law. Haemopoietic tissue persisted longer the more premature the infant.

(3) Although hepatic haemopoiesis receded in the last few weeks of gestation this process was hastened by premature birth. In contrast, renal maturation was not hastened by premature birth.

(4) Iron pigment was found in the livers of half the stillborn infants and in the spleens of over one-third of them.

(5) Infants dying from one to three days after birth often had less visible iron in the liver and spleen than those dying earlier. After three days the visible iron rose progressively in amount for about two weeks to a maximum value at which it remained for several months.

(6) Siderosis was present in over two-thirds of the livers, and although frequently associated with the presence of haemopoiesis, occurred more often in its absence. The degree of siderosis in the liver and spleen was fairly closely correlated. In the liver the distribution of iron pigment bore no relationship to the amount. There was some evidence that hepatic haemopoietic tissue increased slightly in the first few hours after birth; likewise one to three days after birth hepatic and splenic siderosis decreased.

Discussion

Hepatic Haemopoiesis in relation to the Postnatal Fall in the Erythrocyte Count. In late foetal life and just after birth the circulating red cells in man are derived from two sources, the liver and the bone marrow. Since hepatic haemopoiesis is diminishing, the number of erythrocytes entering the circulation from the liver will fall and, after a time lag depending upon the life span of these cells, the fall in erythrocytes will be reflected in the red cell count of the circulating blood. Thus diminution of hepatic haemopoiesis is one of the factors contributing to the fall in the red cell count in early neonatal life. The importance of this factor cannot be estimated properly until we can distinguish between the red cells produced by the liver and those produced by the bone marrow.

Grüneberg (1942, 1947) in his study of the anaemia of flexed-tail mice has shown that three types of red cell, which succeed each other during development, can be distinguished. In the mouse and the rat primitive red cells which are large (about 12μ in diameter) and mostly nucleated are produced in the yolk sac. These are followed by smaller cells, about 8μ in diameter, mostly non-nucleated and produced by the liver and spleen; these are intermediate cells which dominate the blood picture in the last third of pregnancy. At about the time of birth a fresh generation of red cells appears (about 6μ in diameter) and this is the definitive generation produced by the bone marrow. Thus, if human haemopoiesis exhibits three generations, as in the mouse and the rat, it seems possible that the erythrocytes arising in the liver differ in size from those arising in the marrow. Findlay (1946) has shown that the mean corpuscular volume is much greater in the foetus of 34 to 42 weeks' maturity than in the newborn, the fall occurring soon after birth, so that after an age of 15 days no infant's mean cell volume exceeds 100μ^3. Similarly van Creveld (1932) has shown that the mean cell diameter of both full term and premature infants falls in the first six weeks following birth. These changes in cell size parallel the postnatal fall in the circulating red cell count (Findlay, 1946) and can readily be explained if the larger cells are derived from the liver and the smaller ones from the bone marrow since, as the larger cells reach the ends of their life spans, they will not be replaced by the atrophic hepatic system. Moreover, the simultaneous presence of two generations of red cells distinguished by size accounts for the anisocytosis present at birth but diminishing in the first six weeks of life (van Creveld, 1932; Smith, 1945).

Barcroft (1946) has suggested that the diminution in cell size is accompanied by a substitution of adult for embryonic foetal haemoglobin. If this is true it may be that the large hepatic erythrocytes contain foetal haemoglobin and the smaller erythrocytes of bone marrow the adult type. On the other hand the cells may contain a mixture of the two haemoglobins (Brinkman, Wildschut, and Wittermans, 1934). Likewise, the change in red cell fragility between the foetal and neonatal period may be due to differing properties of the two generations of cells. Thus Findlay (1945) found that the blood of the foetus shows a diminished resistance, but in the newborn child the resistance is increased.

Mollison's (1948) observations on the survival of placental blood transfused into newborn babies support this concept of heterogeneity of neonatal

blood. He showed that for about ten days after transfusion the donated cells disappeared more rapidly than cells of an adult donor; after ten days the rate of disappearance of placental and adult cells was the same. He concluded that a small proportion of the infantile cells disappeared more rapidly than adult erythrocytes. It would be interesting to know if the larger erythrocytes have the shorter life span.

The postnatal fall in the red cell count and haemoglobin concentration is usually attributed to excessive haemolysis following birth (Parsons, 1933; Smith, 1945). This has been denied by Findlay (1946) and a diminished rate of formation suggested by Josephs (1932). One of the main difficulties in accepting this theory of excessive haemolysis is that no adequate mechanism has been suggested. Davidson *et al.* (1941) write : 'The excessive destruction of erythrocytes which characterized the neonatal period appears to be caused by release from foetal anoxaemia.' A similar view was expressed by Wollstein (1938) who also explained the siderosis of the liver and spleen as a result of the iron freed by destruction of haemoglobin. It is a curious idea that a full oxygenation of blood *in vivo* should result in excessive haemolysis; there is no *in vitro* evidence to suggest such a possibility. Fallon (1943), without citing her evidence, attributes the postnatal fall in erythrocytes to increased phagocytosis of the red blood corpuscles consequent on increased oxygen supply at birth. Mitchell (1928) reported the presence of haemolysin in the maternal serum which can affect cord blood, but this could not be confirmed by Goldbloom and Gottlieb (1930). Engelhardt (1947) has suggested that the postnatal haemolytic mechanism is similar to that of a normal adult. The agent is lysolecithin, which is found in the blood of the newborn in comparatively large amounts. The action of lysolecithin is inhibited in the first few days of life by oestrone and as this falls there is an increase in cholesterol. The rise in the cholesterol level is not enough to check blood destruction owing to a simultaneous rise in lecithin. This theory needs critical examination and replication of its experimental basis before it can be accepted.

The evidence in favour of excessive haemolysis is based on (*a*) the occurrence of siderosis of the liver and spleen in the neonatal period, (*b*) the development of bilirubinaemia, and (*c*) certain experimental evidence.

Siderosis of the Liver, Spleen, and Kidney. Brückmann and Zondek (1939) have reviewed the life curves of iron in the liver and kidney which have been reported by various workers. Ramage *et al.* (1933) using spectrographic methods showed that the average iron content of human foetal livers in the first 24 weeks of gestation is 0·21% of dry weight, at full term is 0·25%, rising to a maximum of 0·374% at one to two months after birth, falling to a minimum of 0·048% at 13 to 24 months. Barcroft (1946) has criticized these results on the grounds that Ramage and his colleagues did not exclude the blood that was in the vessels in their estimations. Barcroft (1946) quotes figures obtained by McDougall on foetal sheep and lambs in which blood was removed from liver slices by washing; these show marked variation in iron content, even between the livers of twins, but there is a general tendency to rise in the second half of pregnancy. Brückmann and Zondek (1939) using a method of estimating non-haemin iron have shown that the iron content of the liver is high in the first two weeks of life averaging 0·177% of dry weight (range 0·030 to 0·290%) falling to a minimum average value of 0·017% at the age of 2 years, after which it rises slowly so that at the age of 20 years the adult level of 0·08% is reached. A similar life curve occurs in the kidney, but at a lower level, the average iron content in the first few days of life being 0·0205%. These results are similar to those of Ramage *et al.* (1933), but at a lower level, since only non-haemin iron is measured, and conform in a general way with my histological findings.

Brückmann and Zondek (1939) write:

> 'The values in the newborn are in general quite high, but there are exceptions. According to the classical theory . . . the newborn has a congenital reserve deposit of non-haemin-Fe, which is to compensate for the lack of Fe in the milk diet of the first few months. But a series of investigations indicates that this is true only in part . . . Some increase in non-haemin-Fe occurs already during foetal life, but the bulk of it is not accumulated until after birth, when the well-known postnatal blood destruction reduces the high haemoglobin values to about 50% within a few weeks, liberating large amounts of Fe.'

An alternative hypothesis is that the high iron content of the foetal liver is not a store laid by for the future suckling phase but a supply immediately available for the present demands of hepatic erythropoiesis. As haemopoiesis diminishes in late foetal life and in the early neonatal period the hepatic iron is less rapidly utilized and therefore accumulates in the liver cells, ultimately reaching a level at which the particles are large enough to be visible when stained by the prussian-blue method. Alongside this process it may be supposed that when the hepatic iron reaches a sufficiently high level and is not used for erythropoiesis, some is drained off and deposited in the spleen. Moreover, if the usual view is taken that siderosis represents excessive haemolysis it is difficult to account for the fact that

nine out of 18 of my stillborn infants showed hepatic siderosis, and Gilmour (1941) found siderosis in younger foetuses.

Gillman and Gillman (1945) have shown that in haemolytic conditions iron appears first in the Kupffer cells and only later in the hepatic cells. In contrast Waterlow (1948) pointed out that in pernicious anaemia iron is mainly present in the parenchyma, and he considers this a condition in which utilization is prevented by lack of liver principle. The bulk of the iron in my cases was probably in the liver cells, but often the Kupffer cells were well filled, and in one liver the iron was almost entirely in the Kupffer cells. Thus the distribution of iron gives no simple explanation of the mechanism of siderosis in the foetus and newly born infant.

Neonatal Hyperbilirubinaemia. The rise in the bilirubin content of the blood and the resulting physiological jaundice are usually attributed to neonatal haemolysis (Wollstein, 1938). However, as Findlay, Higgins, and Stanier (1947) have pointed out, whereas bilirubinaemia usually reaches its maximum in the first week of life and thereafter decreases, the fall in the erythrocyte count and haemoglobin content are greater in the second week when the bilirubin level is falling; moreover, the rate of fall in the erythrocyte count and haemoglobin is the same in the icteric group of infants as in the non-icteric. They concluded that excessive haemolysis is not the cause of icterus neonatorum. During intra-uterine life bilirubin may be removed from the foetus by means of the placenta and by excretion through the liver. Ÿlppö (1913) denied that foetal bilirubin is normally excreted by the placenta since the maternal plasma bilirubin level is not raised during pregnancy. Findlay *et al.* (1947) pointed out that the amount produced by the foetus each day is so small that it could not appreciably affect the maternal blood level. Moreover it has been shown that the bilirubin level in the umbilical artery of newborn babies is higher than in the umbilical veins (Cserna and Liebmann, 1923; Findlay *et al.*, 1947). At birth the placental excretion is suddenly cut off and the burden thrown on the liver. Thus, unless the excretory capacity of the liver is sufficient, the blood bilirubin level may be expected to rise. Davidson *et al.* (1941) analysed Ÿlppö's data and showed that the less the bilirubin content of the first meconium the greater the intensity of the subsequent icterus. Similarly, Findlay *et al.* (1947) have re-examined Ÿlppö's data and showed that the greater the bile content of the faeces during the first five days of life the less the jaundice. They give data collected by themselves indicating that the more severely jaundiced babies excreted less bilirubin in the faeces than the less jaundiced. Both these groups of workers concluded that the degree of neonatal bilirubinaemia is a function of the maturity of the liver. Further, Findlay *et al.* (1947) showed that the more premature the infant the more likely it was to develop jaundice, which may reasonably be expected if maturity of liver function is an important factor.

Experimental Observations. Goldbloom and Gottlieb (1930) kept guinea-pigs in a chamber under reduced pressure for about one month. The haemoglobin and red cells increased as in acclimatization to high altitudes. When the animals were returned to normal atmospheric conditions the haemoglobin and the red cell level fell to normal in about five days and the icteric index immediately rose. Conditions in the chamber were supposed to correspond to those *in utero* and removal from the chamber be analogous to birth. Thus the fall in haemoglobin and erythrocyte count and the rise in the icteric index appeared to correspond to the changes in neonatal life. Examination of their protocols shows that in three of their 11 experiments the bilirubin was raised before the animal left the chamber, and in the others the maximum bilirubin level was reached immediately after removal from the chamber and then fell. These did not therefore correspond to the findings in neonatal life. It may be that the period of reduced pressure corresponded to the life span of guinea-pig erythrocytes, in which case an increased breakdown would have occurred near the end of the period of exposure. Findlay *et al.* (1947) suggested that anoxaemia might have caused liver inefficiency. Further, the conditions in the chamber were not those of intra-uterine life, especially with regard to the blood carbon dioxide level (Barcroft, 1946).

Dynamic Haematology. From this discussion it may be concluded that there is no direct evidence of excessive haemolysis occurring soon after birth and that all the indirect evidence is capable of an alternative, or better, explanation. Until the changes in the infant's blood are analysed in terms of dynamic haematology, as attempted by Grüneberg (1942) for the anaemia of flexed-tail mice, we shall not know what part, if any, is played by excessive postnatal haemolysis. To make such an analysis it will be necessary to know (*a*) the changes in blood volume at birth, (*b*) the rates of production and wastage of both the hepatic and marrow erythrocytes, (*c*) the constancy, or otherwise, of the mean cell size of the two generations of erythrocytes. It must also be remembered that the infant is growing and that newly formed erythrocytes not only replace loss by normal wastage but add to the size of the circulating erythron. A number of these factors

have been studied, e.g., the growth of the circulating erythron (Findlay, 1946) and blood volume (Lucas and Dearing, 1921; Smith, 1945; Grüneberg, 1941) but such information is not sufficiently extensive for an adequate analysis.

Mechanism of Haemopoietic Recession in the Liver. Any discussion of this mechanism is at present speculative. It may be that in foetal life haemopoietic activity is maintained at a high level by anoxaemia, as in adaptation to high altitudes, but the higher carbon dioxide content and tension of foetal blood may play a part. With the onset of pulmonary respiration at birth the oxygenation of the blood rises and thus the stimulus to proliferation of the hepatic haemopoietic system falls. The recession of haemopoiesis in the last few weeks of gestation is not an isolated phenomenon. It is at this time that subcapsular development of new glomeruli ceases; the pregnanediol and oestrone excretion starts to decline and shows violent fluctuations (Hain, 1942), and in animals there is a rapid accumulation of glycogen in the liver (Needham, 1931; Schlossmann, 1938; Windle, 1940).

Siderosis in Malnutrition. Helmholz (1909), Lubarsch (1921), and Saito (1924) have described siderosis of the liver and spleen in infants dying in a state of malnutrition. Waterlow (1948) described siderosis and found the non-haemin iron content raised in the liver and spleen of infants dying in the West Indies of undernutrition and 'fatty liver disease'. He ascribed these changes to failure to utilize iron since he could find no evidence of haemolysis, the bilirubin content of the blood being raised only in the presence of liver damage. The distribution of the siderosis was similar to that I have described. Waterlow's results show the same trend as those of Brückmann and Zondek (1939), namely a fall in non-haemin iron in the liver with increasing age, but his results are all much higher than those (which he uses as controls) of Brückmann and Zondek. His observations would have been more convincing had he run a series of controls of his own for comparison. Andersen (1938) found siderosis of the liver in 14 of 19 infants dying of cystic fibrosis of the pancreas before the age of 6 months; after the age of 6 months the incidence diminished. The infants I have described showed marked siderosis of the liver and spleen with a slight tendency to diminish between the ages of 4 and 7 months, and this was a continuation of foetal and neonatal siderosis. It seems probable that the siderosis of infants which is ascribed to malnutrition is really a physiological process.

Summary

There are two types of hepatic haemopoietic recession: (*a*) an intra-uterine type, most marked in the last weeks before birth, and (*b*) an extra-uterine type which succeeded birth after a lag period of one to three days.

Extra-uterine atrophy followed an approximately logarithmic law.

The mean time of disappearance of haemopoietic tissue from the liver of full term infants was about eight days after birth, and for infants born eight to 13 weeks premature 37·6 days.

Siderosis of the liver and spleen was present in both foetuses and infants born alive. After the first three days of life the degree of siderosis rose progressively to a maximum in about two weeks; it remained at this level for some months.

The literature contains no well-established evidence that the postnatal fall in the erythrocytes count is due to excessive haemolysis.

The evidence given here suggests that the postnatal fall in the erythrocyte count is, in part, due to atrophy of erythropoietic tissue in the liver.

Evidence from the literature suggests that the cells produced by hepatic erythropoiesis have different properties, such as size and life span, from those derived from bone marrow.

In the foetus and newly born infant iron brought to the liver is used in haemopoiesis. When haemopoiesis diminishes after birth the iron accumulates giving rise to siderosis. Some of the excess iron is probably removed and deposited in the spleen.

Siderosis described in infants dying of malnutrition is probably of no pathological significance.

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NEUROFIBROMATOSIS PRESENTING AS MACROGLOSSIA

BY

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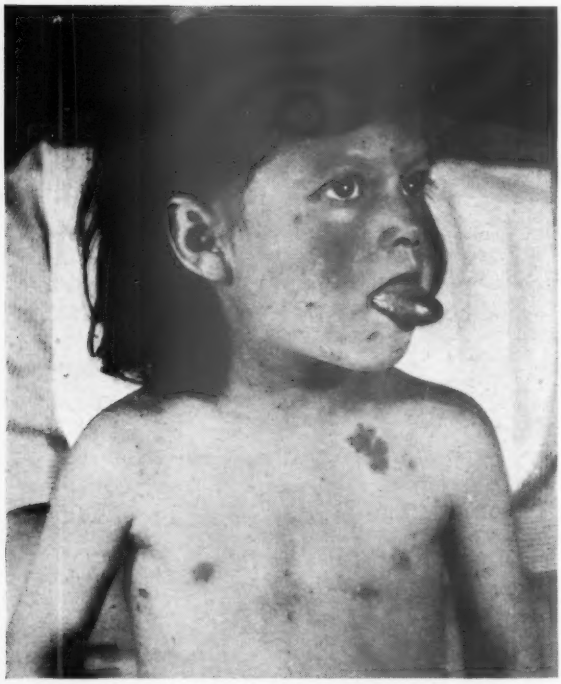

FIG. 1.—Patient showing neurofibromatosis of tongue and café-au-lait patches.

Case Report

Joyce K., aged 6, is the tenth of 12 children. The remainder of the family are healthy and there is no family history of any condition suggesting neurofibromatosis.

Birth was normal and infancy uneventful, but the mother noticed a large and slightly protruding tongue when she first saw the child a few hours after birth. She had gastro-enteritis at 6 months, but apart from this had no serious illness. She was bottle fed and no difficulties occurred, but development seemed a little slow. She did not walk until she was nearly 2, and has always been backward at school.

The tongue gradually and very slowly enlarged, and she came up to hospital in March, 1949, because it was noticed to be interfering with her speech. Pale brown patches had become apparent on the skin of her chest and shoulders at the age of four.

On examination she was a thin, puny child with a moderate kyphoscoliosis and a protruding abdomen. There were numerous café-au-lait patches on the chest, shoulders, and abdomen, and a number of small, shotty, subcutaneous nodules could be felt in the left supraclavicular region. The tongue was much enlarged, the enlargement consisting of a diffuse tumour mass involving mainly the right side (Fig. 1).

A wedge-shaped excision of part of the tongue was carried out on June 6, 1949. The child made an uninterrupted recovery from the operation and her speech has been much improved, though further increase in size has occurred since operation, and in addition, the supraclavicular nodules have become larger and more easily felt.

Section of the removed portion of the tongue showed the characteristic appearances of neurofibromatosis (Fig. 2).

Discussion

Neurofibromatosis is a disease of many and varied manifestations, from Treves' elephant man to small local lesions, and if all its major and minor manifestations are considered together, is not an uncommon condition. Von Recklinghausen, in his monograph published in 1882, integrated the four main features; the skin tumours of mollascum fibrosum, the fusiform neurofibroma, the plexiform neuroma, and the café-au-lait patch. And he pointed out their common pathogenic background which he called a 'growth perversion of the foetal neuro-ectoderm.' There is usually evidence of a hereditary tendency in which sometimes not only the disease but the localization seems to be genetically determined. For example, Gardner and Frazier (1930) described familial nerve deafness due to neurofibroma, in which 38 members of one family were affected. There is commonly a certain degree of mental defect.

Before the publication of von Recklinghausen's monograph neurofibroma of the tongue associated with multiple cutaneous lesions was described in a paper published by Robert Smith in Dublin in 1849, and a detailed account of the clinical and pathological features of a case was presented to the London Pathological Society by Abbott and Shattock in 1903. Müller (1933), describing a case, suggested the name macroglossia neurofibromatosa congenita for the condition.

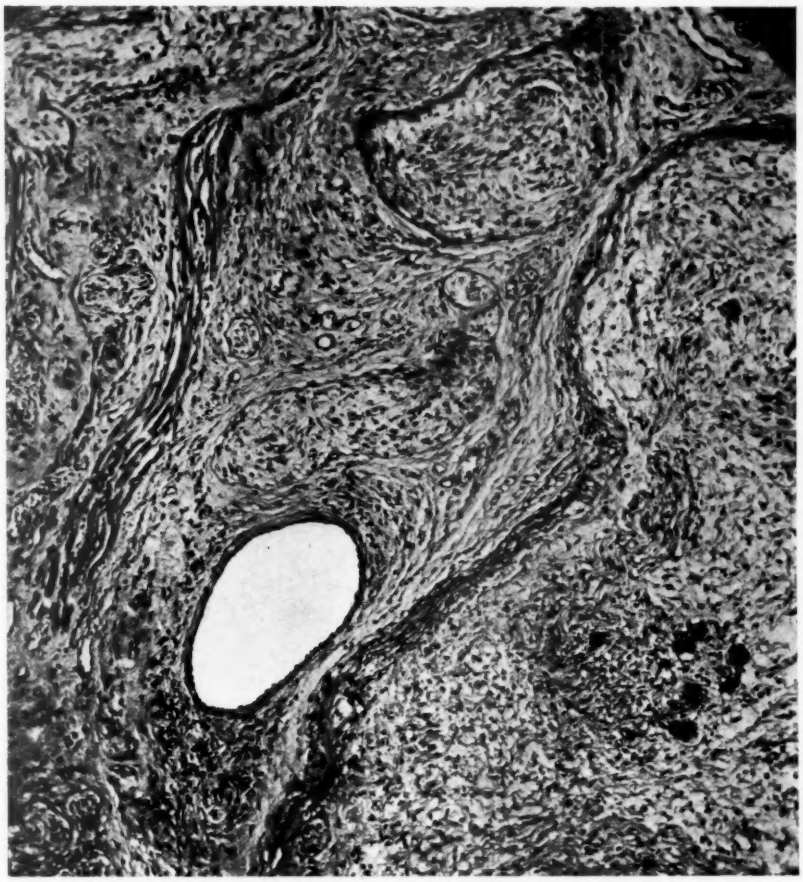

FIG. 2.—Section of neurofibroma of tongue (×65).

Neurofibromatosis presenting in infancy as macroglossia is thus a well recognized condition, but is sufficiently rare to justify this report.

Acknowledgments are due to Dr. J. Mills, pathologist to the Royal Berkshire Hospital, and to Professor Dible, in whose department at the Postgraduate Medical School the microphotograph was taken.

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TUBERCULOUS PERICARDITIS*

BY

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(Received for Publication February 2, 1950)

Tuberculous pericarditis was formerly thought to be an uncommon condition, but the more recent recognition of the tuberculous aetiology of many cases of chronic constrictive pericarditis (Sellors, 1946; Edwards, 1948; Parsons-Smith, 1948) should stimulate us to attempt the diagnosis of tuberculosis of the pericardium in its earliest stages.

The incidence of the disease is generally considered to be approximately 1% of all necropsies and 3% of patients dying from tuberculosis (Sweeney, 1940). A review of the literature of the past 50 years suggests that the frequency of tuberculous pericarditis has steadily increased. This trend is seen when the incidence is expressed as a percentage of all necropsies, as well as a percentage of tuberculous conditions (Table 1), but necropsy records in all probability do not reflect the true incidence because complete healing of the tuberculous pericardial lesion may occur. The clinical recognition of tuberculous pericarditis may also be difficult, and some of the cases of pericarditis diagnosed as rheumatic are probably tuberculous in nature. Furthermore, the symptoms of tuberculous pericarditis may be so mild that the patient does not seek medical advice, and even if suspected, the diagnosis may not be confirmed either by guinea-pig inoculation or by biopsy of the pericardium.

The case now to be described has many of the common features of the disease but is unusual because a caseous gland had ruptured into the pericardium.

Case Report

G.B., a boy aged 5 years, had measles six weeks before admission to hospital. He seemed to recover completely within two weeks, but one week later an irregular fever developed, associated with a slight cough and wheeze. Subsequently he had bouts of abdominal pain and vomiting. The bowels were regular and there was no disorder of micturition. He was an only child, his mother and father were well, and there was no family history of tuberculosis. Before the attack of measles he had enjoyed good health.

On admission he had a temperature of 100° F., pulse rate was 140 per minute and respiration rate 26 per minute. His tongue was moist, and the throat reddened, but no enlarged glands were felt in the neck. The left side of the chest showed diminished movement, and the percussion note was impaired over the left chest anteriorly, in the left axilla, and to the right of the sternum. The breath sounds were tubular in the left axilla. The heart was enlarged, the apex beat being in the left fifth intercostal space outside the mid-clavicular line, and the heart sounds were soft and distant. There were no bruits but a friction rub was heard down the left border of the sternum. No abnormality was detected in the abdomen, and the urine

Table 1

Frequency of Tuberculous Pericarditis over 50 Years

Author	Year	Total Necropsies (All Ages)	Tuberculous Conditions	Cases of Tuberculous Pericarditis		
				Total	Percentage of All Necropsies	Percentage T.B. Necropsies
Osler ..	1893	1,000	275	7	0·7	2·5
Norris ..	1911	7,219	1,780	82	1·1	4·6
Blalock and Levy	1937	1,653	—	42	2·6	—
Suzman ..	1943	1,893	102	6	0·32	5·9

* Paper read before the Liverpool Paediatric Club on November 18, 1949.

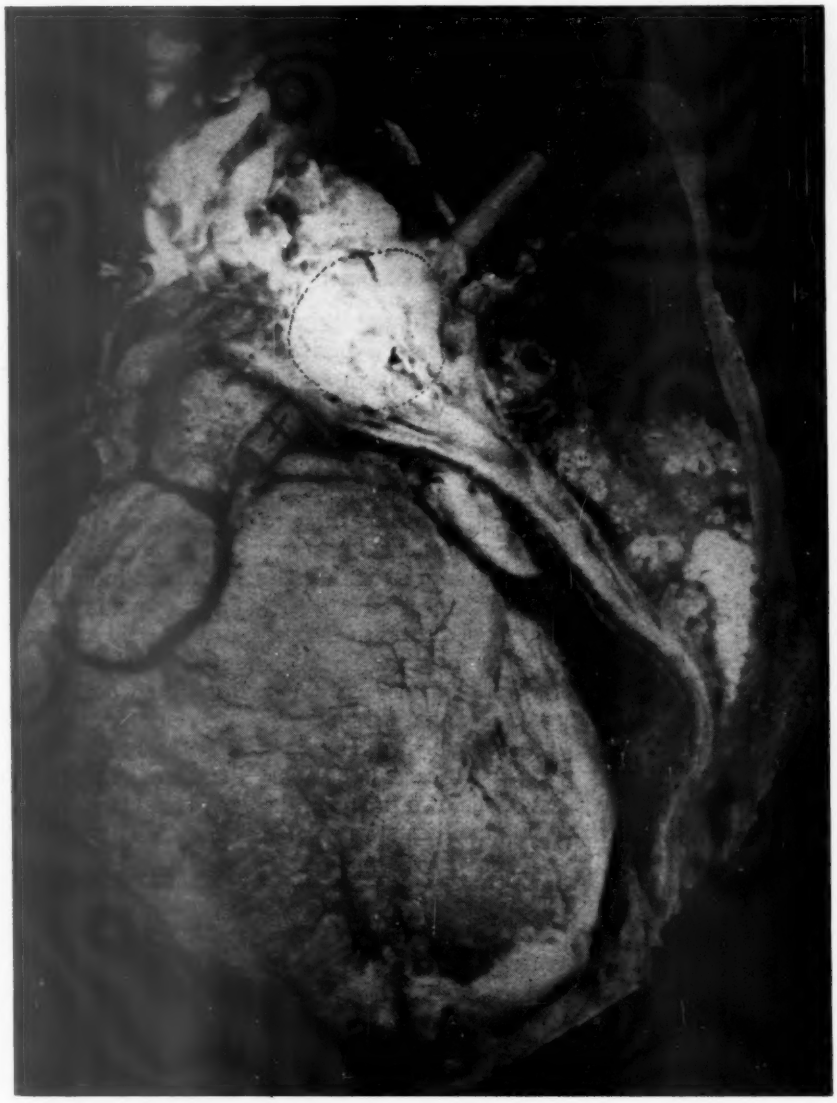

FIG. 1.—Heart showing tuberculous pericarditis. The caseous gland is outlined and a glass rod (X) is in the position of the fistula between this gland and the pericardial sac.

was normal. A radiograph of the heart on the day of admission showed a pericardial effusion and consolidation at the left base. The electrocardiogram showed simple tachycardia only, with normal voltage. The Mantoux test in a 1 in 10,000 dilution was positive after 48 hours (1 cm. erythema with small central wheal). On the day after admission 20 ml. of greenish-yellow fluid were aspirated from the pericardial sac. This fluid contained a small number of lymphocytes. Tubercle bacilli were not seen or grown on culture. Penicillin (200,000 units) was injected into the pericardial sac at the initial and subsequent aspirations, from none of which were tubercle bacilli isolated. Pericardial fluid accumulated rapidly in spite of repeated aspirations, the neck veins became congested, the liver became enlarged, and operative drainage of the pericardium was advised.

At operation the pericardium was immobile and on palpation the cardiac pulsation was minimal. When the pericardium was incised approximately 20 oz. of greenish-yellow fluid gushed out and the cardiac pulsations became visible.

A portion of the pericardium was removed and the histological report was as follows:

The granulation tissue arising from the pericardium was heavily infiltrated with chronic inflammatory cells, and the presence of numerous epithelioid follicles supported the diagnosis of tuberculous pericarditis. Tubercle bacilli were not found.

Subsequently the wound became secondarily infected and death occurred 36 days after operation.

NECROPSY. Necropsy was performed 18 hours after death. A cavity, 3 cm. in diameter, discharging offensive light green pus, was present over the lower end of the sternum slightly to the left of the midline.

The dura was tense, and the brain (320 g.) was congested.

On elevation of the sternum it was apparent that the cavity led directly into the pericardial sac which contained about 10 ml. of purulent fluid. The visceral and parietal layers of the pericardium were covered with thick purulent exudate of a green colour, and there were light adhesions between the heart and diaphragm. There was no pleural fistula. The under surface of the sternum just cephalad to the drainage wound showed scanty tubercles. At the extreme left upper zone, lateral to the pulmonary artery and in the position of the ductus arteriosus, there was a fistula 2 mm. in diameter leading into a caseous lymph node which was adherent to the parietal pericardium (Fig. 1).

The pleural cavity of the right lung contained a few millilitres of clear yellow fluid. There were recent adhesions between the anterior border of that lung and the pericardium. Tubercles were visible when the surfaces were separated.

The anterior portion of the upper lobe of the left lung was firmly adherent to the pericardium, and in the portion overlying the heart there was a caseous focus

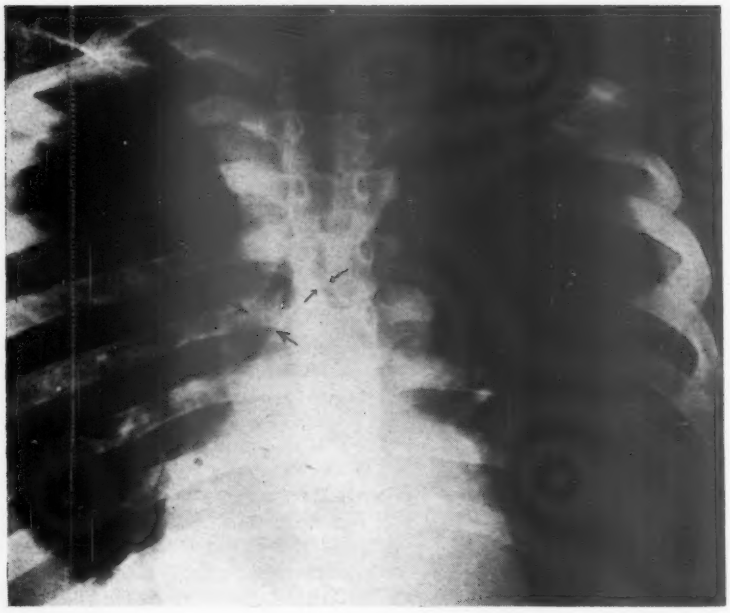

FIG. 2.—Tomogram (A.P. view) to compare the diameter of the normal right main bronchus and the narrowed left main bronchus.

approximately 3 by 2 cm. There was caseous bronchopneumonia of the left lower lobe.

There were 50 ml. of clear yellow fluid, with small fibrin clot, in the peritoneal cavity. Tubercles were observed on the under surface of the diaphragm above the spleen. The gastro-intestinal tract was healthy. The spleen (75 g.) was firm and congested. The liver (752 g.) was firm, and showed marked nutmeg mottling. The kidneys, adrenals, and mesenteric glands were normal.

MICROSCOPY. The liver showed marked fatty infiltration, largely peripheral in distribution with light portal infiltration of lymphocytes and plasma cells.

The spleen showed scanty areas of caseation with early giant cell formation, blending, without a marginal lymphocytic zone, into the surrounding pulp.

The pericardium consisted of granulation tissue showing varying degrees of organization and dotted with soft tubercles showing central caseation, grading into the surrounding tissue without a defined lymphocyte border. There were also deposits of fibrin with intense polymorph infiltration indicating an added pyogenic inflammatory reaction.

Section of the caseous area of the left upper lobe overlying the heart showed a cavity lying centrally in a zone of caseating lung tissue, and surrounded by caseating tuberculous bronchopneumonia. The portion of the left lower lobe sectioned showed the features of tuberculous bronchopneumonia.

The brain showed no evidence of tuberculous meningitis.

FIG. 3.—Tomogram showing the outline of the two main bronchi and glandular pressure on the left main bronchus.

Discussion

Some writers consider that tuberculous pericarditis may be either primary or secondary to tuberculosis elsewhere. Blatt and Greengard (1928) state that primary tuberculous pericarditis, in the strict sense of the term, is extremely rare, and Ellman (1945) considers that it does not exist for all practical purposes. Furthermore, it is unreasonable to assume that inhaled or ingested tubercle bacilli will cause disease of the pericardium only and not of adjacent organs. The probable explanation is that the primary focus was so small and had healed so completely that it has become unrecognizable macroscopically. Thompson (1933), however, collected 21 cases from the literature and added seven of his own in which the pericardial lesion was the only manifestation of tuberculosis. These cases

were in adults between the ages of 49 and 84 years. In Harvey and Whitehill's (1937) 34 cases, there was only one case of primary tuberculous pericarditis in which the mediastinal glands were not caseous, the lungs were normal, and no tuberculous focus was found elsewhere.

Secondary tuberculous pericarditis may occur in one of the three following ways. First it may occur as part of a miliary spread and usually presents no clinical evidence during life. Such a condition was observed in a girl of 12 years with tuberculous meningitis, in whom the visceral pericardium was studded with miliary tubercles as part of the generalized miliary dissemination.

Secondly it may be caused by lymphatic spread from a caseous lymphatic gland, the route which is considered by most observers to be the commonest by which the pericardium is involved.

Osler (1893) held that tuberculous pericarditis was due in the majority of instances to infection of the pericardium through lymphatic channels by retrograde spread from caseous mediastinal glands. One of his cases was a boy aged 5 years, another was a boy aged 16 years, and the oldest was a man of 72 years. Kinney and Douglass (1937) also emphasized the importance of mediastinal gland tuberculosis in the aetiology of tuberculous pericarditis. Blalock and Levy's 42 cases (1937) all had tuberculosis of mediastinal nodes, and Heimann and Binder (1940) found tuberculous root glands in all their 31 cases. Barrett and Cole (1944) described a male patient aged 22 years who was found at necropsy to have, in addition to tuberculous pericarditis, a caseous tuberculous gland near the left bronchus between the main left pulmonary artery and the arch of the aorta. The gland was situated at 1·5 cm. from the pericardium at its nearest point, and no definite track between gland and pericardium was apparent.

Suzman's (1943) case of a man of 23 years showed caseous glands at both hila, and he concludes that 'in this case the primary focus was a tuberculous gland in the mediastinum secondarily affecting the pericardium; and later as the disease progressed, further dissemination occurred, causing generalized miliary tuberculosis.'

The third route is direct extension from an inflamed mass of hilar glands or pleura. This may also give rise to tuberculous pericarditis but is usually considered to be a most unusual mode of origin.

One of Osler's cases (1893), a man of 39, had a mass of caseous glands adherent to the pericardium. In Keefer's (1937) 20 cases, 11 had enlarged tuberculous mediastinal glands and 'in several the pericardium had become involved as a result of rupture of a caseous lymph node directly into the pericardial sac.' In others there was evidence that the process had extended to the pericardium from the pleura, the lung, or even the peritoneum. Among these cases there was only one detailed case report which described the rupture of a gland directly into the pericardial sac.

Seligman and Lederer (1940) reported a case of acute suppurative pericarditis in a woman of 54 years which had resulted from the perforation of a pyogenic abscess in a tracheobronchial lymph node and in which the tubercle bacilli were found in the wall of the gland draining a fibrotic pulmonary Ghon focus.

Smellie (1925) reported a similar happening in a girl of 8 years. She had caseous glands in the superior mediastinum, at the tracheal bifurcation, and in both lung roots. Almost all the caseous material had been extruded from the bifurcation gland, leaving a cavity about $1\frac{1}{2}$ in. $\times$ $\frac{7}{8}$ in. A secondary infection with *Bact. coli* had taken place. There was a pin point perforation into the pericardium with localized suppurative pericarditis.

Among Harvey and Whitehill's (1937) 95 cases is a report of a man of 64 with tuberculous pericarditis which arose from the rupture of a caseous gland into the pericardium.

Churchill (1937) found an extrapericardial tuberculous abscess containing 1 oz. of pus at operation for constrictive pericarditis on a man who had suffered from tuberculous pericarditis in early life. This abscess was situated external to the pericardium but perforating into it, suggesting that a suppurating tuberculous mediastinal lymph node had at one time set up a transient tuberculous effusion which had healed, or possibly, that the lymph node abscess had by contiguity caused a pericardial reaction resulting in scar formation.

These examples of tuberculous pericarditis caused by rupture of a caseous lymph node are the only ones I have been able to trace in an extensive search of the literature, and they support the view of Hannesson (1941) that 'pericarditis as a result of direct extension of infection from a neighbouring focus is most uncommon.'

In the patient I have described, the gland which ruptured into the pericardial sac was the gland (Engel's gland) of the ductus arteriosus (Engel, 1947). In a further case of tuberculous pericarditis treated at St. Thomas's Hospital by Dr. Goadby this same gland was enlarged.

Case Report

The patient was a boy of 14 years admitted to hospital with a severe, non-productive cough of one month's duration. He had a temperature of 102° F., there were

signs of pericardial effusion, and this diagnosis was confirmed radiologically. Over the course of three weeks the patient's condition gradually improved, although there was intermittent fever and his pulse averaged 120 per minute. Seven weeks after admission the patient was allowed up for the first time, having had a normal temperature during the preceding month and an average pulse rate of 88. His condition, however, deteriorated and he developed a tachycardia of 120 and an irritative reflex cough. Two weeks later he was allowed up once more but the cough and increasing congestion of the neck veins and liver required further bed rest. At this time x-ray screening was performed, and it was noticed that the left side of the chest was more expanded than the right, its movement was greatly decreased, and the whole lung field was noticeably more translucent than the right. A glandular shadow was seen opposite the arch of the aorta and tension emphysema due to partial obstruction of the left main bronchus was diagnosed. The tomograms confirmed this diagnosis (Figs. 2 and 3).

Thoracic surgeons (Edwards, 1949) are aware of the thinness of the pericardium in the region of the ductus arteriosus when they operate for patency of this structure, but I am doubtful if it can be argued from this that the pericardium of patients with normal obliteration of the ductus might also be thin at this point. In fact it could be reasonably held that the normal fibrosis of the ductus would result in an increased thickness of the pericardium in this area.

At Alder Hey Hospital the gland of the ductus arteriosus was present in eight out of 10 consecutive necropsies. Its size was variable and up to 1 cm. in length. The gland was situated anterior to the ligamentum arteriosum and overlapped the pericardium to a variable degree (Fig. 4). The node was separated from the pericardium by very loose areolar tissue. A similar arrangement was found posteriorly where the interbronchial node overlapped the pericardium, though not so frequently. The fold of pericardium in the vicinity of the ligamentum arteriosum was found to be slightly thinner and of looser texture than that over the phrenic nerve area of the left ventricle, though the difference was not very great.

The gland of the ductus arteriosus drains a relatively small area of lung, namely the apex of the left upper lobe, but it frequently contains caseous material even when no tuberculous focus occurs in its drainage area. The following two post-mortem reports illustrate this point.

At necropsy on a boy of 3 years with tuberculous meningitis a caseous focus was shown a third of the way along the fissure separating the left upper lobe from the lower lobe. There was a caseous gland at the hilum in relation to the upper lobe bronchus and the gland of the ductus arteriosus overlying the reflection of the pericardium was also involved: it was firm and white with scanty caseous areas.

At necropsy in a child of 2 years with tuberculous meningitis adhesions showed between the medial aspect of the upper lobe of the left lung and the mediastinum over an enlarged lymph node 1½ cm. × 1 cm. lying against the pericardium at its point of reflection from the pulmonary artery. The lymph node was caseous and showed areas of calcification. At the inferior border of the upper lobe approximately half way along there was a small caseous focus. Similar lesions were present in the left lower lobe. The most probable explanation is that the gland of the ductus arteriosus was

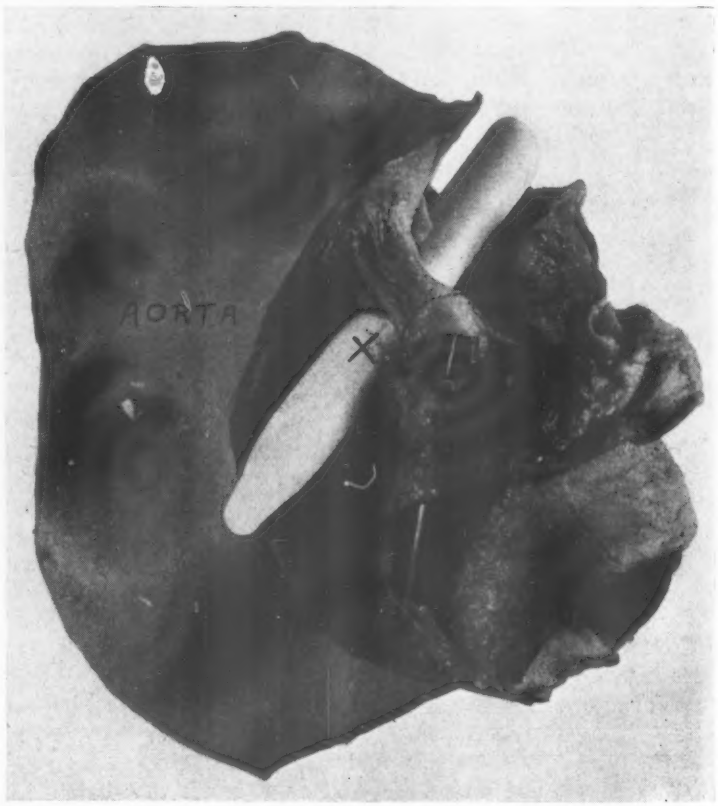

FIG. 4.—Post-mortem specimen demonstrating the gland of the ductus arteriosus (Engel's gland) which has been reflected to the side, the original position being marked with interrupted lines. The opened aorta is on the left, and a marker (X) is placed behind the ligamentum arteriosum. The other marker is in the fold of pericardium on which the gland is situated.

secondarily involved by spread from neighbouring lymphatic glands.

Summary

Tuberculous pericarditis is still considered to be a rare disease in childhood but the recognition at operation of the tuberculous nature of a high proportion of cases of constrictive pericarditis suggests that the disease may occur more frequently than it is diagnosed.

Even when suspected the diagnosis is difficult to confirm either by guinea-pig inoculation or by biopsy of the pericardium.

The primary and secondary types of tuberculous pericarditis are discussed, and the clinical details of a case of tuberculous pericarditis resulting from the rupture of a caseous gland adherent to the pericardium are described together with other cases in which the gland of the ductus arteriosus (Engel's gland) was responsible for the spread of tuberculosis to the pericardium. The involvement of this gland may be merely fortuitous but the anatomical situation of the gland, contiguous with the pericardium at its reflection, would readily facilitate pericardial involvement.

I wish to express my thanks to Dr. E. G. Hall, pathologist at Alder Hey Hospital, for the detailed pathological investigations; to Dr. H. K. Goadby for permission to refer to one of his cases; and to Professor Norman B. Capon for his advice and criticism.

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TUBERCULOUS ISCHIO-RECTAL ABSCESS AND PRIMARY PULMONARY TUBERCULOUS COMPLEX IN A FIVE-MONTHS-OLD INFANT

BY

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(RECEIVED FOR PUBLICATION MARCH 20, 1950)

The occurrence of a tuberculous ischio-rectal abscess complicating a primary pulmonary focus in a five-months-old infant is considered sufficiently unusual to warrant the following description.

Case Report

The baby weighed 5 lb. 9 oz. at birth. He was breast fed for two months, and then changed to a dried milk mixture. His weight gain was moderately good, he was lively, his appetite was satisfactory, and he had not been constipated. At the age of 1 month he developed a cough which had persisted, and at the age of 5 months he developed a 'boil' on his left anal margin which would not heal.

The child's mother and two siblings were well, but his father, who lived at home, had open pulmonary tuberculosis.

When first seen, at the age of 29 weeks, the child weighed 14 lb. 8 oz., was well hydrated, and did not appear ill. Apart from some pallor the only abnormality found was a punched-out, oval ulcer, measuring ¾ in. by ½ in. with undermined, dusky blue edges, at the left anal margin (Fig. 1). The ulcer base was filled with soft, ragged, pale granulations. Exploration with a probe revealed a ¾ in. long track running medially to a cavity adjacent to, but not communicating with, the rectum. The rectal mucosa was normal on proctoscopy.

The child had a low grade pyrexia (up to 100° F.). His Mantoux reaction, 1:10,000, was positive. The sedimentation rate was 37 mm. in the first hour. A blood count gave Hb. 63%; red cells 4·1 million; white cells 15,000 per c.mm (P. 44%, L. 52%, M. 4%). Repeated examinations of stomach washings and stools for acid-fast bacilli were negative. A swab from the ulcer yielded a coagulase positive *Staph. aureus*, but no tubercle bacilli. No culture or guinea-pig inoculation was carried out. A punch biopsy (Fig. 2) from the ulcer edge showed numerous giant cell systems, and in a Ziehl-Neelsen preparation moderate numbers of acid-fast bacilli were seen within the giant cells in all the sections examined. A chest radiograph showed a right middle lobe collapse (Fig. 3), which, at bronchoscopy, was found to be due to compression of the middle lobe orifice from without. The carina was flattened, and no endobronchial lesion was seen.

Treatment consisted of the daily intramuscular

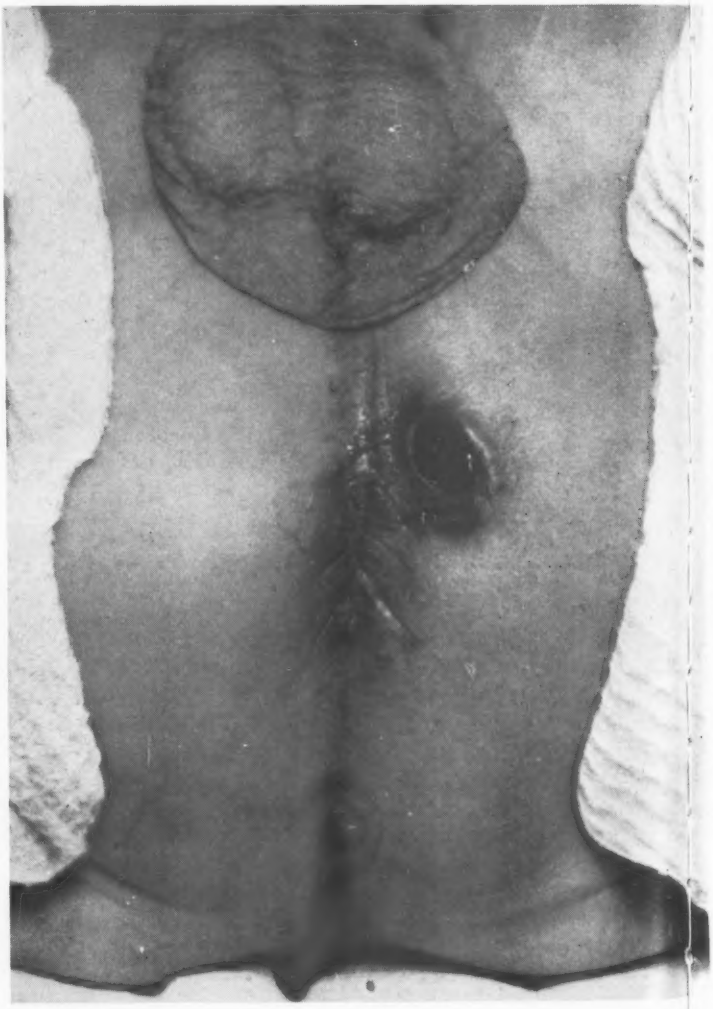

FIG. 1.—Tuberculous ischio-rectal abscess in a five-months-old baby.

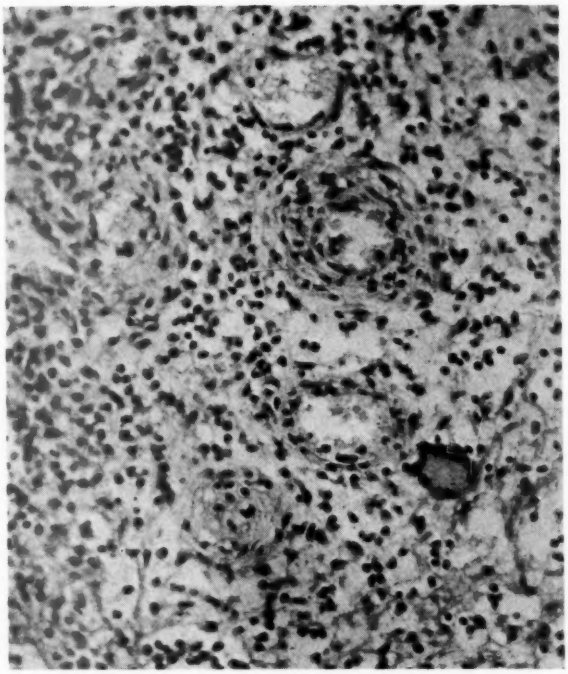

FIG. 2.—Photomicrograph of punch biopsy showing a giant cell. Haematoxylin and eosin. × 220.

injection of 0·36 g. streptomycin for eight weeks; the local application of a paste containing P.A.S. 20 g., sulphathiazole 5 g., Haldane's emulsifying base ad 100 g.; and an iron mixture by mouth. As no ischio-rectal fistula was present, it was decided that surgical intervention was unnecessary. On this treatment the ulcer healed in a month, the pyrexia subsided, the anaemia disappeared, and the child gained weight. The middle lobe collapse has now persisted for seven months.

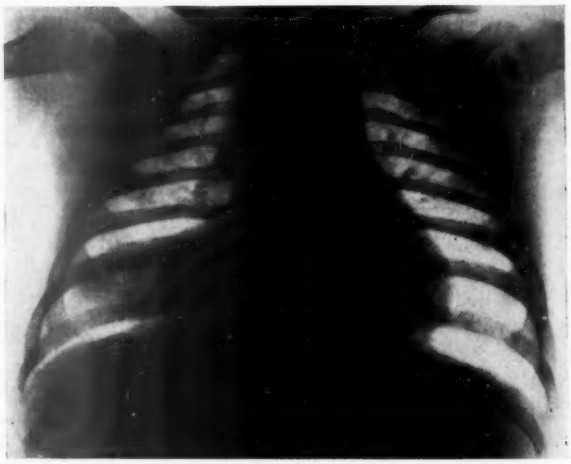

FIG. 3.—Radiograph showing right middle lobe collapse.

Discussion

Reports on the incidence of tuberculous ischio-rectal ulceration in cases of pulmonary tuberculosis vary widely. Granet (1940) found that perianal infections were ten times more common in tuberculous subjects than in the non-tuberculous, but considered that they arose primarily as non-specific infections with secondary tuberculosis superadded. This view is shared by Zadikoff (1947) who found that 28·9% of 1,000 cases of pulmonary tuberculosis had rectal lesions. Aronsson (1948), in a study of 356 cases of anal ulceration in tuberculous patients found the incidence to be between 2·5 and 5%. Few authors mention the age of their patients, but Goorwitch (1942) could find only one 15-year-old patient recorded in the literature, and added a 13-year-old patient of his own. In all these the rectal ulceration was a complication of open pulmonary tuberculosis, and no reference could be found to patients with a primary pulmonary tuberculous focus, that is, a 'closed' focus, associated with a tuberculous ischio-rectal lesion.

All authors draw attention to the difficulty of proving the tuberculous aetiology of perianal infection in tuberculous patients. Martin, Lansford, and Sweany (1940) point out that the mere presence of acid-fast bacilli in perianal lesions does not prove their tuberculous aetiology, as patients with pulmonary tuberculosis swallow their sputum. According to Martin and Sweany (1940) a 33% error arises if reliance is placed solely on culture or inoculation experiments. Though foreign body giant cells do occur in simple pyogenic ischio-rectal lesions (Henschen, 1924), most authors agree that the demonstration by histopathological methods of acid-fast bacilli in association with giant cell systems is adequate proof of the tuberculous nature of the lesion (Jackman and Buie, 1946; Aronsson, 1948).

Summary

A case of a primary pulmonary tuberculous complex, complicated by an ischio-rectal abscess, is reported in a five-months-old child. The tuberculous nature of the perianal lesion was proved by histopathological methods.

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BILE PIGMENTS IN THE STOOLS OF INFANTS

BY

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In the normal person bilirubin is converted in the gut into stercobilin. However, unaltered bile pigment occurs in meconium and in the stool of any individual with much intestinal hurry, and has also been shown to be passed at times by some older infants, though this fact does not seem to be widely known. The absence of stercobilin from the stool is usually taken as evidence for total biliary obstruction, and infants with unduly prolonged neonatal jaundice may thus be suspected of having atresia of the bile ducts. Such children have been transferred to this hospital where the absence of stercobilin has been confirmed, but abundant bilirubin has been found in the stools. These children have made a spontaneous recovery.

The Present Investigation

It was decided to take a random sample of infants under 4 months of age who were not suspected of having obstructive jaundice and to test their stools for bilirubin and stercobilin.

The methods used were the qualitative ones described by Harrison (1947). Fouchet's reagent was used to detect bilirubin, and a spectroscopic examination was made for stercobilin. These tests are quick and simple to perform and are probably the ones most used in England at the present time. They are not very delicate, but it was felt that this was an advantage, since we wished to discover whether a normal infant could ever produce a stool containing so little pigment that it could not be qualitatively detected by these usual tests. Ladd (1935) pointed out that babies with total biliary atresia may pass a small amount of pigment, which presumably reaches the interior of the gut either in bile-stained digestive secretions or by desquamation of jaundiced epithelial cells. In our experience of these cases the qualitative tests used in this investigation have always given either a totally negative result or indicated only a very faint trace of pigment.

One hundred and two infants admitted to the hospital were tested, some on several occasions, and where stercobilin was absent at the first test, further specimens were examined at intervals until the pigment appeared, or until the baby died or was discharged.

Results

Stercobilin was not detected in the stools of 23 children. Of these, 21 gave a negative reaction at the first test, and two gave a similar reaction when the pigment had previously been present. Neither of these two children had diarrhoea or jaundice at the time. Another child gave negative tests up to the 161st day of life, a positive being recorded on the 167th day.

Fourteen of these 23 children were observed to develop a positive test for stercobilin. Coincidentally the bilirubin reaction became weaker or negative.

No stool (in over 160 tests) was devoid of both pigments.

Of the 102 children, 21 were totally breast-fed up to the time of the test, and all gave a positive Fouchet test in their stools. The stercobilin results are shown according to age distribution in Table 1.

Table 1

Analysis of Stercobilin Results

Age (weeks)	0–4	5–8	9–12	13–15	16–20	20+	Totals
Stercobilin +	1	9	1	1			12
Stercobilin —	3	3	1		1	1	9

It will be readily seen that a negative stercobilin test was common in the first weeks; in fact, of the six youngest children in the series, only one (aged 4 days) showed a spectroscopic band of stercobilin. It was absent in 43% of all the breast-fed cases.

There were 81 children who had been bottle-fed to some extent before the test. Many had been partially or totally on the breast at an earlier period. Bilirubin was found in the stools of about half (40 cases). Where it was present in small quantity, stercobilin was always found, but where there was a large amount of bilirubin, stercobilin was usually

absent. Table 2 shows the stercobilin results in age groups.

TABLE 2

STERCOBILIN RESULTS ACCORDING TO AGE GROUPS

Age (weeks)	0–4	5–8	9–12	13–16	17–20	Totals
Stercobilin +	15	20	22	7	5	69
Stercobilin —	4	3	3	2		12

Stercobilin was therefore absent from less than 15% of the stools of bottle-fed babies at the first test. This finding was unusual even in the first month of life, but did occur in normal children up to at least 16 weeks of age.

Combining the two tables, the total figures reached are those of Table 3.

TABLE 3

COMBINED STERCOBILIN RESULTS

Age (weeks)	0–4	5–8	9–12	13–16	17–20	20+	Totals
Stercobilin +	16	29	23	8	5		81
Stercobilin —	7	6	4	2	1	1	21

The colour of the stools was not a reliable index of the pigment content. Several pale green stools gave a negative Fouchet's test, and three whitish specimens contained stercobilin. The stercobilin-negative and bilirubin-negative stools showed the same wide range of colours.

No significant correlation was found between stool pigment and any particular condition for which admission to hospital had been advised.

Discussion

It is obvious that testing for stercobilin alone cannot prove jaundice to be obstructive in an infant. Our results indicate that either bilirubin or stercobilin is always present in the stool of a normal child, and that tests for both pigments must be used. The absence of both is strong evidence for total biliary obstruction. Further, it is possible in normal infants for stercobilin to disappear temporarily. The two babies in whom this occurred were bottle-fed at the time, and stercobilin remained absent for two and three weeks repectively.

The unreliability of the stercobilin test is greater in the first two months of life, and greater in breast-fed than bottle-fed babies.

Comparison of Tables 1 and 2 suggests (though the figures are not large enough to do more) that bilirubin normally persists for some time in the stools of breast-fed babies; that stercobilin is absent at least as often as it is present in breast-fed infants under one month old; and that stercobilin tends to appear earlier in bottle-fed babies.

It has been known at least since 1840 that unchanged bile pigments may predominate in the stools of newborn infants (Simon). Since that time the pigment excretion in the faeces has been studied by various workers, and Schorlemmer (1900) pointed out that stercobilin appeared later in the stools of breast-fed than artificially fed babies. Isolated observations have been made of bilirubin being present for long periods—up to 14 months (Giaume and Lanza, 1929)—but it usually disappears earlier than this. Certainly the age by which bilirubin disappears from the stool is variable and may depend on the bacterial population of the gut, and this in turn may be affected by the diet and manner of feeding.

A number of quantitative studies of faecal pigment excretion have been made since Ylppö (1913) estimated the bilirubin output in the first 14 days of life. Snelling (1933) studied the urobilinogen (stercobilin) excretion. Ross, Waugh, and Malloy (1937), in an investigation of icterus neonatorum, made quantitative estimations of the pigments in the stools and urine of normal babies in the first week of life. All 35 babies investigated showed measurable quantities of both urobilin and bilirubin throughout the first week. In fact, their figures were startingly higher than those of earlier workers, ranging from 11·5 to 57·5 mg. of bilirubin per day, and from 33·5 to 69·3 mg. of urobilin per day. Tat, Greenwalt, and Dameshek (1943) in a similar investigation found far smaller amounts, their figures for the first five days being from 1 to 23 mg. (average 8·6 mg.) per day of bilirubin, and from a trace to 0·7 mg. of urobilin per day. Thus they found about a quarter as much bilirubin and a fiftieth as much urobilin. These discrepancies are remarkable. It is perhaps significant that there are so many different methods for the estimation of these pigments, and this may reflect their unreliability. At any rate, no group of workers in this field has used methods identical with those employed by others. It would seem that the problem of the quantitative excretion of bile pigments needs more exhaustive investigation.

Behrendt (1949) in his work on diagnostic tests for infants and children states that in the differential diagnosis of jaundice 'in over half of the cases, the diagnosis of obstructive jaundice can be made by analysing the urine for bilirubin and urobilinogen.' He neither discusses the value of tests on the stools nor describes any method for detection of stool pigments, nor does he describe how the diagnosis of obstructive jaundice is reached in the cases where urinary analysis is inconclusive.

The tests employed in this investigation are easy to perform, quick and widely used in this country, and the results show that so long as both tests are employed it is improbable that a case of neonatal jaundice will be falsely labelled obstructive.

Summary

Over 160 stools were tested from 102 infants under 4 months of age without obstructive jaundice. In 20% of babies stercobilin was not detected. It is therefore necessary to test for both bilirubin and stercobilin to prove biliary obstruction in children of this age group.

I should like to express my deep indebtedness to Dr. W. W. Payne for his help and advice in this work, and to his technical staff for their unfailing co-operation.

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SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

BY

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In the course of the past year three cases of subcutaneous fat necrosis of the newborn have been seen and followed up. They presented features interesting enough to warrant description, particularly as some of them may help to shed light on the still obscure aetiology of the disease.

Case Reports

Case 1. A male infant was admitted to hospital on August 4, 1949, at the age of 3 weeks because his mother had noticed a number of small reddish-purple 'lumps' on his thighs during the week preceding his admission. He was the third child of healthy parents, the other children being well. His weight at birth was 9 lb. 2 oz. The delivery was normal, labour having lasted 24 hours, but the infant showed signs of asphyxia and required resuscitation. He recovered quickly and was able to feed from the breast in the course of the first 24 hours. Examination on admission showed an infant in good general condition (weight 10 lb. 6 oz.). There was slight desquamation of the skin of the abdomen and back. On the flexor aspect of both thighs there was a symmetrically placed indurated area, bluish-red in colour, with a raised edge, extending over the deeper structures of the thigh. The indurated edge seemed to extend about 1 cm. in depth and could be firmly gripped between the examining fingers. Smaller areas of similar appearance were noticed on both calves. Nothing else abnormal could be detected. The temperature was 99·2° F.

During the first two days the condition was regarded as an acute inflammatory lesion and was treated with intramuscular penicillin, 100,000 units eight-hourly. However, new areas of induration appeared at the site of the penicillin injections, involving the lateral and extensor aspects of the thighs. Penicillin treatment was therefore discontinued and oral sulphamezathine therapy substituted. A tentative diagnosis of subcutaneous fat necrosis was made at this time.

In the course of the succeeding week new lesions of similar appearance but varying size appeared. The areas now affected were the sacral, the gluteal, the lateral part of the back, and the skin over and below both scapulae. On the eleventh day after admission a biopsy of the skin and the subcutaneous tissues of the left thigh was carried out.

Biopsy Report. An inflammatory reaction was present in the subcutaneous fat, most marked immediately below the dermis but not extending therein, but appearing rather as finger-like processes into the fat. The cellular reaction consisted mostly of large cells with ill-defined cytoplasm and pale oval nuclei (probably histiocytes); a few polymorphs and lymphocytes were present. A number of giant cells could be seen, not of foreign body type but consisting of three or four nuclei in an ill-defined basophilic cytoplasm. The lipid in some of the fat cells included in these areas appeared to have broken down giving rise to fatty acid crystals arranged radially. Arteries penetrating the subcutaneous fat tended to show an acute periarteritis.

The child's general condition remained good, though his temperature showed almost daily fluctuation between 100° F. and 98·8° F. Towards the end of the fourth week, when some of the indurated areas seemed to be regressing, he was discharged home. His weight had been steadily rising. He was seen in the out-patient department one month later. The involved skin had returned to normal apart from a small area on the extensor aspect of both thighs, but on the lateral surface of the right thigh overlying the trochanter a depressed area was noticeable. This subsequently presented as a deep groove due to atrophy of the subcutaneous fat (Fig. 1). The overlying skin was normal but firmly fixed

Fig. 1—Atrophy following subcutaneous fat necrosis.

to the underlying structures. Physical and mental progress had been satisfactory throughout.

Case 2. A boy, aged 2 days, was admitted to hospital because of severe cyanosis which developed shortly after birth. Oxygen was administered and an injection of coramine was given into the thigh. Pregnancy, labour, and delivery had been normal. Birth weight was 7 lb.

Examination revealed a well-developed, plump infant, somewhat distressed and with a hoarse cry. The face appeared extremely congested and small petechiae were visible on the forehead and cheeks. Respiration was rapid. The temperature was 101° F. There was a purulent discharge from the nose and eyes, and a foetid smell, although the infant was perfectly clean. Slight desquamation of the hands and feet was noticed. The percussion note over the right axilla was impaired. No other pathological findings could be elicited. A diagnosis of atelectasis was made and this was confirmed radiologically, the radiograph of the chest also revealing a right-sided pneumothorax.

Penicillin and streptomycin were administered intramuscularly into the thighs for the first three days, when streptomycin was discontinued and penicillin continued by mouth.

During the first few days the infant was kept in an oxygen tent and the cyanosis improved considerably. The temperature returned gradually to normal in the course of the first week. At the beginning of the following week a firm, reddish-purple swelling of the right lower buttock developed, which extended some way into the panniculus adiposus. Three days later a similar indurated area appeared in the other buttock, firmly attached to the skin and showing the ' orange-peel ' sign on attempting to lift up a fold of skin. The indurated area was raised slightly above the level of the normal skin, was not tender, and felt rather warmer than the rest of the skin. There was no fluctuation. After three weeks the infant's general condition had greatly improved, the pneumothorax had been absorbed, the atelectatic lung had re-expanded, cyanosis and dyspnoea had disappeared, but the induration of the buttocks still persisted. The gain in weight was satisfactory and the infant was discharged. He was seen regularly at fortnightly intervals, and after approximately two months the induration had completely cleared and the baby appeared well and healthy.

Case 3. A female child was delivered by difficult forceps extraction. Severe asphyxia was present and was treated with lobelin (injected into the cord) and oxygen. The infant responded quickly. The weight at birth was 10 lb.

On the twelfth day there appeared a hard, reddened mass on the anterior part of the right upper arm and several smaller reddened and indurated areas like nodules in the skin of the right side of the neck below the mastoid. In the course of the following week three further indurated areas were noticed in the subcutaneous tissue over the right deltoid.

The baby's well-being was not affected, feeds being taken well, and weight gain was adequate. At the end of the third week she was discharged. Two months later the affection of the skin and subcutaneous tissue had entirely disappeared.

Discussion

Bojlen and Petri (1936), discussing the aetiology of fat necrosis of the newborn, support the prevailing view that birth injury is of major importance (Bernheim-Karrer, 1926; Marfan and Hallez, 1926). Zeek and Madden (1946), summing up the opinions of various authors, give six points regarded as contributory: (1) obstetric trauma; (2) low temperature, causing fat to solidify so that it acts as a foreign body; (3) deficiency of olein in the fat tissue of the newborn, also causing fat to solidify; (4) the presence of an abnormal lipolytic ferment; (5) glandular dyscrasia; and (6) combinations of several of these factors.

Against birth injury being of importance in the aetiology of fat necrosis it is pointed out by Fischl (1931) that obstetric injury is common whereas fat necrosis is certainly rare. Obstetric trauma will not account for its appearance in infants delivered by Caesarean section. Gray (1926) recorded its occurrence antenatally.

Considering the history of the cases reported here, it is striking that each of them was asphyctic at, or shortly after, birth. In Cases 1 and 3 this was due to difficult delivery, whilst in Case 2 it was the result of atelectasis and pneumothorax. It is therefore suggested that anoxaemia resulting from asphyxia may be a predisposing element, though certainly not the only one. Asphyxia was present in Unshelm's (1932) case delivered by Caesarean section, as well as in an infant reported by Woringer and Weiner (1928). The occurrence of asphyxia *in utero* offers an explanation for those cases reported as having developed the disease before birth.

Among the 14 cases of Scandinavian authors reviewed by Bojlen and Petri (1936) the presence of asphyxia at birth was stressed in more than half of them, but the obstetric data in the remainder are not complete. The patients of Fischl (1931), Kohnstam and Herbert (1927), Zeek and Madden (1946), Flory (1948), Harrison and McNee (1926), Bernheim-Karrer (1926), McIntosh, Waugh, and Ross (1938) also suffered from various degrees of asphyxia. In its wider sense asphyxia can be included among the birth injuries, so that the same objection may be raised against its being of aetiological significance regarding its relative frequency compared with that of fat necrosis in the newborn. It is therefore likely that anoxaemia only prepares the way and that one or more additional factors so far unknown are necessary for the development of the characteristic clinical changes.

A low-grade pyrexia was encountered in the three cases here reported as well as in a large number of those previously cited. An increase in the white blood cells with polymorphonuclear preponderance was noted in Case 1, persisting beyond the period during which it is physiological. Case 2 showed a leucopenia of 2,000 with 90% polymorphonuclear cells in the differential count.

Often there is an associated infection, as in Case 2, and those of Fischl, Harrison and McNee, Zeek and Madden, and others. It is possible that fat necrosis is the direct response of adipose tissue, already damaged by anoxaemia, to an infecting agent or is an allergic reaction to a localized infection. Trauma, such as obstetric manipulations or, as in Case 1, penicillin injections, may also be a contributing factor.

The histological picture in Case 1 agrees with the findings of Harrison and McNee, Bojlen and Petri, Zeek and Madden, and Davis and Brain (1947), and indicates an inflammatory reaction mainly in the tissue between the fat lobules. It has been suggested that this may be a response to the necrosed fat acting in the manner of a foreign body.

The low olein content of the fat tissue of the newborn or the correspondingly greater palmitic acid value can hardly be accepted as of aetiological importance, since the findings apply to all newborn infants. No evidence of a lipolytic enzyme has been produced so far, nor has any glandular dyscrasia been encountered.

A case of relapsing febrile nodular non-suppurative panniculitis in a young child was described by Larkin, De Sanctis, and Margulis (1944). The distribution of the lesions was similar to that of fat necrosis of the newborn. Spain and Foley (1944), Ungar (1946), and Mostofi and Engleman (1947) demonstrated that the typical histological changes of Weber-Christian disease were not confined to the subcutaneous panniculus but were to be found throughout the adipose tissue, epicardial, peripancreatic, perirenal, periadrenal, mesenteric, omental and pretracheal fat, being involved. As a further characteristic of Weber-Christian disease, atrophy of the subcutaneous fat with attachment to deeper structures has been pointed out (Johnson and Plice, 1949). Zeek and Madden (1946) and Flory (1948) discovered that fat necrosis in their cases was not limited to the subcutaneous structures but was scattered throughout the fat tissues of the body affecting the perithymic, perirenal, periaortic and peribronchial fat as well as that situated round the ribs, pancreas, and mesentery. Case 1 showed a marked degree of atrophy of the fat tissue similar to that reported in the cases of Weber-Christian disease, only it was more pronounced.

Though histologically the fat tissues in nodular panniculitis show a more extensive cellular infiltration and the inflammatory process is more active than in fat necrosis, they are essentially similar. No fat crystals have been found in panniculitis, but this may be a reaction peculiar to the fat tissues of the newborn, due to its different composition. Harrison and McNee (1926) have expressed the opinion that fat necrosis may be a primary inflammation of the adipose tissue, a point of view which is supported by the clinical features of the disease, its febrile course, the association with an increase in the polymorphonuclear cells, the development of new lesions many weeks after birth, its appearance in infants of good general condition, and the similarity to febrile relapsing non-suppurative nodular panniculitis.

Summary

Three cases of fat necrosis in the newborn are reported, and the various aetiological factors discussed.

Anoxaemia resulting from asphyxia is suggested as the most likely predisposing element.

Fat necrosis of the newborn is regarded as an inflammation of the fat tissues not limited to the subcutaneous panniculus adiposus, and points of similarity with Weber-Christian disease are stressed.

My thanks are due to Professor Wilfrid Gaisford for his most valuable advice and criticism.

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THE ASSESSMENT OF RESULTS IN THE CONSERVATIVE TREATMENT OF CEREBRAL PALSY

BY

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In order to assess the progress made by a child undergoing treatment for the physical defects associated with cerebral palsy, it is necessary to adopt a scheme which is simple, easy to work, capable of alteration and, above all, free from ambiguity. Such terms as 'improved,' 'making progress,' mean little or nothing and lead to a dangerous self-deception on the part of those employed in any scheme of treatment. Complicated assessments sooner or later succumb to human error and become observed in the breach. Inelastic schemes need constant recasting.

The following procedure is based on the use of skill charts very similar to those designed by Phelps. It will be seen that these charts are expressed entirely in terms of physical functions and that these functions are of the simplest form, but are, at the same time, fundamental for complete physical ability. In this scheme the skill charts are of two kinds, viz., physiotherapy charts and occupational therapy charts. This merely represents the division of the work undertaken by the two departments, and the arrangement can be altered where no occupational therapy department exists. The physiotherapy charts show the functional ability of the lower limbs and trunk muscles rather than that of the upper limbs, though, for a few, upper limb movement is also necessary. On the other hand, the occupational therapy charts are almost exclusively concerned with upper limb and neck function. Taken together they give a very fair idea of a child's physical ability and, if any one is missing, he cannot be said to possess normal function. Each child should be tested every month and the charts filled up accordingly. If necessary, graphs of the progress made in selected functions can be drawn, and are particularly useful in stimulating a child's interest in his achievement. There are, of course, obvious criticisms. For instance, a child may be able to perform the necessary movement, but the quality of that movement may not be good. Nevertheless, quality can be learnt only after the movement can be performed. Again, a child may be able to perform 127 of the total of 128 skills and yet not walk downstairs without aid. It is, however, very unlikely that one missing function would persist when all the others had been learnt.

Skill Tests

Physiotherapy

ROLLING

Back to abdomen over R. arm.
Back to abdomen over L. arm.
Abdomen to back over R. arm.
Abdomen to back over L. arm.
Back to either side.
Abdomen to either side.

CRAWLING

Prone: can hold head, shoulders, and chest off floor momentarily.
Prone: can sustain the above.
Prone: can hold L. hip off floor.
Prone: can hold R. hip off floor.
Prone: can hold both hips off floor momentarily.
Prone: can sustain the above.
Prone: can progress using arms only.
Can support weight on all fours momentarily.
Crawls and reciprocates limbs to move along.
Supine: flexes knees and reciprocates to progress.

SITTING

Tailor fashion with support at hips only.
Tailor fashion, alone momentarily.
Tailor fashion, sits alone.
Sits in straight chair unsupported and untied.
Sits unsupported on stool.

RECIPROCATION

Has active assisted leg reciprocation in lying.
Has active leg reciprocation lying.
Reciprocates legs while standing with support.
Reciprocates legs while standing without support.

Physiotherapy (cont.)

BALANCE

Pulls from sitting to standing.
Kneels unsupported momentarily.
Kneels unsupported.
Supports own weight with help.
Supports own weight holding furniture.
Stands unsupported momentarily.
Stands unsupported.
Has R. leg balance momentarily.
Has R. leg balance sustained.
Has L. leg balance momentarily.
Has L. leg balance sustained.
Knows correct way to fall.
Regains standing position after falling with help.
Regains standing position after falling without help.

WALKING (with and without callipers recorded separately)

Walks holding on to furniture.
Walks in parallel bars.
Walks and turns in parallel bars.
Walks on skis with assistance.
Walks and turns on skis unaided.
Walks with doll's pram.
Walks with minimal support.
Walks unaided on floor.
Walks unaided on pavement.
Walks unaided on grass.
Walks 50 steps in one minute.
Walks upstairs with help.
Walks upstairs holding rail.
Walks upstairs without aid.
Walks downstairs with help.
Walks downstairs holding rail.
Walks downstairs without aid.
Walks with correct posture.

Occupational Therapy (right and left hands recorded separately)

FEEDING

Can grasp spoon.
Can release grasp on spoon.
Can pick spoon from table.
Can take hand to mouth.
Can take spoon to mouth.
Can put food into mouth from spoon without spilling.
Can take all the food from spoon into mouth.
Can use fork.
Can use a spoon and fork.
Can use a knife and fork.
Can put biscuit or sandwich into mouth.
Can drink from mug, cup, or glass half filled.
Can drink from mug, cup, or glass filled.
Can drink through a straw.

DRESSING

Can take off sock.
Can put on sock.
Can take off pullover.
Can put on pullover.
Can undo large buttons.
Can undo small buttons.
Can do up large buttons.
Can do up small buttons.
Can take off cardigan.
Can put on cardigan.
Can take off shoes.
Can put on shoes.
Can lace up boot.
Can tie a knot.
Can tie a bow.
Can knot a tie.
Can brush and comb hair.
Can fix grip or slide in hair.

DRAWING

Can keep hands flat on 15 sq. in. paper.
Can draw a circle inside a 2 in. square.
Can draw inside $\frac{1}{2}$ in. square.
Can draw recognizable objects.
Can hold paper still when drawing.
Can turn pages of book.
Can sit on ordinary chair at ordinary table when drawing.

Procedure

In the completed table showing the progress made by 34 children at present in St. Margaret's School, it will be seen that the physiotherapy and occupational therapy skills have been added together. This has been done purely to save space. At St. Margaret's School these records are kept separately, and it is possible to see at a glance where the incidence of the handicap is greatest, and whether the child is responding better to one or other of the two forms of therapy. This arrangement shows where alterations in treatment schedules should be made. Taken over a period of years it should be possible to gain a reasonable idea of the types and ages likely to benefit most.

Examination of the figures in Table 1 provides some more general information, although its value is limited by several factors: (1) The groups of cases of different types are small. (2) The patients are a selected group of children over 5 years old, with handicaps which had prevented them from going to school but were not severe enough to make them bedridden. They are not subject to frequent epileptic attacks. These children were chosen because they appeared, when examined by a paediatrician and myself, usually with the help of a psychologist, to offer the possibility of a good response to treatment. Furthermore, they are the patients who were at the school in December, 1949. One who was admitted in that month has been omitted, and also 18 who improved enough to go to other schools before December, 1949. Of a further 13 discharged before that date three went

to other institutions for cerebral palsy and 10 were discharged as unsuitable for treatment and represent early errors in selection. (3) With this set of tests, it is easier to make a large numerical advance from an initial low score than from a high one. Thus the 16 children with initial scores of 9-75 improved on the average by 28, while for those with initial scores of 76 to 104 the figure was 12. Due allowance for this must be made in considering improvement in relation to other factors. For example, age may affect the degree of improvement, although one would not expect it to do so in children over 5 years old, as almost all the skills are normally acquired at a much younger age. The 13 children aged 4-5 years improved by an average of 25 skills, but their average score on admission was 70. The 20 older children improved by 17, but their average initial score was 79. (4) The duration of treatment must affect the results if treatment is effective at all (Table 2).

TABLE 1

EVALUATION OF SKILLS BEFORE AND AFTER TREATMENT

Case No.	I.Q.	Age on Admission (Years)	Skills on Admission (Possible Maximum 128)	Duration of Treatment (Months)	Added Skills After Treatment
Hemiplegia					
1	93	5	78	18	19
2	116	6	95	11	10
3	92	6	104	9	2
4	70	8	56	34	24
Paraplegia					
5	116	5	103	6	3
6	93	5	62	27	40
7	90	7	65	35	28
8	90	5	73	3	30
9	76	7	98	19	8
10	94	7	95	3	3
11	118	4	76	37	28
Spastic Tetraplegia					
12	107	5	66	27	34
13	114	10	67	32	23
14	85	7	34	35	31
15	85	6	69	27	32
16	90	5	59	27	39
17	120	6	84	6	14
18	120	4	61	3	5
19	91	7	91	20	13
20	92	7	96	6	8
Athetoid Tetraplegia					
21	90	5	65	34	36
22	140	7	79	34	25
23	140	8	82	9	9
24	137	7	77	6	10
25	109	5	37	34	36
26	116	9	94	20	9
27	100	6	76	20	25
28	90	11	73	37	27
29	115	6	9	30	25
30*	84	5	68	26	39
31*	75	7	90	5	7
Ataxia					
32	103	9	98	9	2
33	98	4	86	6	15

* Tension athetoid.

TABLE 2

EFFECT OF DURATION OF TREATMENT ON NUMBER OF SKILLS ACQUIRED

Duration of Treatment (years)	No. of Patients	Average No. of Skills Acquired
Under 1 ..	13	9
1–1½ ..	5	15
2–3½ ..	15	31

Intelligence

The intelligence quotients of these children were calculated after repeated testing by Miss E. M. Dunsdon and Mrs. H. Clark working independently. In most cases the difference between the estimates was small. In Table 1 the mean of the intelligence quotients obtained by the two observers is stated. In 18 children the I.Q. was between 70 and 99 (average 88); in the other 15 children it was 100 to 140 (average 119). The two groups were fairly evenly balanced in respect of age, type of paralysis (Table 2), number of skills on admission, and duration of treatment (Table 3). Contrary to

TABLE 3

AVERAGE INCREASE OF SKILLS RELATED TO DURATION OF TREATMENT

I.Q.	Average Duration of Treatment (months)	Average Score on Admission	Average Increase with Treatment
70–99	21	77	22
100–140	17	74	18

expectation, the average increase in the score of skills was not lower in the children with low I.Q.s than in the highly intelligent children. This observation, based on the performance of a small selected group of children, none of whom was mentally defective, is perhaps not generally applicable, but one is so accustomed to the idea that high intelligence is needed if a child with cerebral palsy is to benefit much from skilled therapy that it is encouraging to find that some of the less intelligent can do well. Doubtless they will not benefit to a similar degree from further education, for these records of skills represent elementary achievements, which are nevertheless of immense practical value.

Types of Disease

In a similar way the progress of cases of different neurological types may be considered. There are too few hemiplegics and ataxics for this purpose, but children with paraplegia, spastic tetraplegia, and athetoid tetraplegia may be compared (Table 4). In paraplegics the effect is difficult to assess as they

TABLE 4

EFFECT OF DURATION OF TREATMENT ON NUMBER OF SKILLS ACQUIRED RELATED TO TYPE OF PALSY

Type	No. of Patients	Average I.Q.	Average Duration of Treatment (months)	Average Score on Admission	Average Increase with Treatment
Spastic paraplegia	7	95	19	82	20
Spastic tetraplegia	9	109	20	70	22
Athetoid tetraplegia	11	109	23	68	23

had already acquired manual skills, and thus had less opportunity to increase their scores. Spastic and athetoid tetraplegics improved about equally, and this again is surprising and encouraging, for we are accustomed to think that spastic tetraplegia holds a much less favourable prognosis compared with athetosis. Evans's (1946) experience that 90% of athetoid and 10% of spastic children are educable may be generally true, but it was not so in this small group.

Summary

A scheme for the assessment of progress in the treatment of cerebral palsy is described. Results obtained at St. Margaret's School since November, 1946, are tabulated. With these tests, it is easier to make a large numerical advance from an initial low score than from a high one.

In these cases greater improvement was observed with prolonged than with brief treatment. Improvement was not less in children with relatively low intelligence quotients than in the more intelligent, and spastic tetraplegia was as suitable for treatment as athetoid tetraplegia.

Sincere thanks are due to Miss P. Mayer, C.S.P., and Miss E. Byard, M.A.O.T., for their help in compiling the statistics.

REFERENCES

Evans, E. S. (1946). *Proc. R. Soc. Med.*, **39**, 6.

BOOK REVIEWS

The Nursing of Sick Children. By E. M. LOVELY, S.R.N., R.S.C.N., S.R.M. 1951. Edinburgh: E. & S. Livingstone. Pp. 120. Price 7*s.* 6*d.*

This is a truly delightful book on nursing, such as one does not often meet in these days, when the theoretical side in the nurse's training is frequently over-stressed to the detriment of the teaching and practice of real bedside care.

To quote from Dr. Forest Smith's foreword: 'It is essentially the recounting of the lesson learnt in the ward by a sister who has spent her life in the care of the sick child, in the training of the young nurse, and in helping the children's specialist in the treatment of his cases.'

Every disorder and illness likely to be met with in a children's ward is described in a few words. But Miss Lovely puts all the stress on the special needs, mental and physical, of the child patient and, with a deep understanding of the child, tries to initiate the young student into the art of thorough observation of the symptoms of disease, maladjustment and discomfort, giving simple but excellent suggestions for their nursing treatment and relief by those commonsense measures which the best nurses will always use in their work.

The approach to the sick child is by way of the normal child, and so this book starts with a section on his development. The premature baby is given a special chapter as are the various systems of the body, each of which are dealt with in turn. There is a short discussion of the administration of drugs and the psychological aspect of a nurse's work in the children's ward.

This book cannot be recommended too strongly—there are so few of its kind. One could hand no better to any student taking up the nursing of sick children, and more particularly to the student nurse who comes to spend a short period in the children's department of a general hospital.

Fevers for Nurses. By GERALD BREEN, M.D., D.P.H. 1950. Edinburgh: E. & S. Livingstone. Pp. 220. Price 7*s.* 6*d.*

This book is eminently suitable for nurses training for the examination of the Register for Fever Nurses. Writing in a plain and uncomplicated manner, Dr. Breen builds up his text by discussing the fundamentals of fever nursing, elementary bacteriology, immunization, and the principles of the prevention of cross-infection. In the initial chapters, nurses are reminded of the simple measures with which a good practical nurse may bring relief and healing to her patient, whilst the medical aspect of each communicable disease is discussed clearly in separate chapters.

The book has recently been brought up to date to keep abreast with the newest therapeutic developments which have, in the last few years, so completely changed the pattern of the management of infectious fevers.

Owing to a possible over-simplification of both style and approach, the more senior nursing student will, however, prefer to use for study and reference Dr. Breen's book for medical students and practitioners.

The 1950 Year Book of Pediatrics. (July, 1949-July, 1950.) Edited by H. G. PONCHER, M.D., with the collaboration of JULIUS B. RICHMOND, M.D. and ISAAC A. ABT, M.D. 1950. Chicago: The Year Book Publishers. 104 illustrations. Pp. 504. Price $5.00.

Last year marked the fiftieth anniversary of this well-known year book, and to observe this occasion each main chapter is preceded by a brief survey, written by an authority, of the achievements of the last 50 years in each particular field. The first of these, on paediatric progress in the United Kingdom, is by the late Sir Leonard Parsons. The rest of the book follows the traditional lines and summarizes the more prominent paediatric papers of the last year.

Thirteenth British Congress of Obstetrics and Gynaecology

The Congress will be held at Leeds, Yorkshire, on July 8, 9, 10, and 11, 1952.

The subjects for discussion are: Abnormal uterine action in labour; stress incontinence of urine; the **place of the paediatrician in a maternity unit;** genital tuberculosis in the female.

All communications relating to this Congress should be addressed to the Secretary: B. L. Jeaffreson, M.D., F.R.C.S., F.R.C.O.G., 32 Park Square, Leeds, 1, England.

The Sixth International Congress of Pediatrics, Zurich, 1950

The third volume prepared in connexion with the sixth International Congress of Pediatrics, with additional abstracts of lectures and all the communications and discussions, is now complete. It will be sent free of charge to all who paid congress fees entitling them to A or C cards.

Others may obtain either the three single volumes for Swiss francs 25.- or the three volumes bound together for Swiss francs 27.-. The two other volumes comprise summaries of communications, and a guide to the exhibition (with notes on the scientific exhibits). The three volumes constitute the Transactions of the Congress and can be supplied from the **General Secretary's Office, International Pediatric Association, Kinderspital, Zürich 32.**

Payments should be made to the account of the Association with the Zürcher Kantonalbank, Zürich.

A certain number of the transactions of the fifth International Congress of Pediatrics, New York, 1947, may still be obtained from Messrs. Almquist and Wiksell, Editors, Uppsala, Sweden, for the reduced price of Swedish crowns 10.-